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# A CRITIQUE OF THE TRANQUILIZING DRUGS, CHLORPROMAZINE AND RESERPINE, IN NEUROPSYCHIATRY*

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THE advent of the tranquilizing drugs has aroused a ferment in psychiatric quarters that to the laity has implied the coming of the millennium in this phase of medicine. In view of the history of previous somatic therapies with similarly enthusiastic claims, it behooves the medical profession to evaluate the present results with a judicial and skeptical eye. It is the purpose of this paper to review the highlights in the literature on these drugs. The paper will be confined to the results obtained through the administration of chlorpromazine and reserpine, since other drugs have been reported in too few cases to be capable of adequate assessment.

## DOUBLE-BLIND STUDIES

Despite the intense optimism expressed by many clinicians concerning the therapeutic efficacy of the drugs, there has been some opinion that the results obtained were due, to some extent, to the enthusiasm that attends the advent of any new therapy on the part of the medical and ward personnel and even of the patients.

A survey of the literature[1-12] shows the publication of about a dozen articles in which the drugs have been tested by the double-blind technic in which, unknown to the personnel dealing with the patients, one group of subjects received the presumably potent agent and the other a placebo. In several cases this initial procedure was followed by an alternation of the drug and the placebo between the two groups,[4,6] and in a few cases by an alternation of chlorpromazine, placebo and reserpine in the same patients.[6,7]

The daily doses of reserpine usually ranged from 2 to 5 mg., but up to 10 mg. was given in one study. The period of medication was usually four to six weeks. The daily doses of chlorpromazine ranged from 100 to 600 mg. but in one study was 800 mg., and the usual period of medication was about eight weeks.

In all these studies, using the double-blind method, except one, either chlorpromazine or reserpine was noted to have effects in behavioral improvement superior to those found in the placebo-treated groups. In the single study[10] in which no difference was found the dose of reserpine (2 mg. by mouth) may have been too small to alter the behavior of the patients. The subjects in these studies numbered about 300 in the reserpine-treated groups, 400 in the chlorpromazine-treated groups and about an equal number in the placebo-treated groups. With the exception of one study,[12] which included 150 patients exhibiting anxiety states, the majority of the other cases were of the chronic schizophrenic type in which the possibility of spontaneous improvement during the short period of study was extremely slight.

There is no question that this review of the literature indicates that the behavioral improvement after the administration of these drugs is definitely beyond that produced by suggestion. Approximately two thirds of the patients showed some degree of improvement on the drug, whereas usually less than a third of the placebo-treated patients showed any improvement and, on the whole, this was to a less marked degree than that in the previous group. Very few striking improvements were noted in the drug-treated group, but this may be attributed in part to the relatively modest dosage and in part to the relatively brief time in which they were employed.

Among these studies were six in which both drugs had been employed in contrast with placebos. Each drug was tested on the same patients[6,7] in two and on different patients in the other four.[3,5,9,11] In five of these studies, one with the same patients[6] and four with different groups of patients,[3,5,9,11] the percentage of improved cases seems to have been about the same for both drugs. In the sixth trial[7] reserpine seemed to give a somewhat higher percentage of improved patients than chlorpromazine — 56 per cent vs. 42 per cent. On the whole, however, in this limited series, the two drugs seemed to be equivalent in therapeutic effect.

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## Schizophrenia

### Dosage

The application of the drugs to schizophrenic patients, who number half the mental-hospital population, is discussed first.

There is not too much uniformity of dosage in chlorpromazine. There have been, in general, three dosage schedules, which may be labeled as low (150-400 mg.),[18-19] moderate (500-900 mg.)[20,21] and high (1000 mg. and up).[22,23] In each group there appears to be roughly the same degree of improvement, though the advocates of the higher dosages claim better results because of this. Sainz,[21] for example, notes that in patients with chronic catatonia receiving 300-500 mg. daily, little if any improvement was seen, whereas 31 of 39 others receiving increasing amounts improved remarkably, 6 showing social recovery. Kinross-Wright[22] advocates an intensive treatment with rapidly increasing dosages up to 4800 mg. daily for eight to ten days.

In general the dosage is usually increased from an initially lower level until the patient has shown improvement, maintained at that level for a varying period and then gradually decreased to a maintenance level. The average dose is about 500-600 mg. daily, divided into three or four doses. The average maintenance dose is about 100-200 mg. daily.

For reserpine the usual dose[24] is initially 5-10 mg. intramuscularly, with about 3 mg. by mouth for a week to ten days, after which, if the patient has improved, the parenteral dose is discontinued. Much higher doses have been given. Sainz[25] has administered 240 mg. of reserpine within twenty-four hours without inducing deep catatonic conditions or significant hypnosis. A diminishing dose is also used as the patient improves. The drug can be given once or twice daily.

### Duration of Treatment

In the acute cases the treatment is maintained until the patient has definitely improved, or up to at least two months. In the chronic cases the treatment should be continued for six to eight months before it is concluded that no benefit is derived. Goldman,[26] for example, notes that in patients hospitalized for less than five years and treated for less than two months, the rate of recoveries and social remissions is 19 per cent whereas in those treated for over two months this value increases to 56 per cent. Similarly, Hollister[27] states that increasing the dose of reserpine from 1-4 mg. daily in one group to 2-8 mg. in another group raised the rate of improvement (moderate to marked) from 30 to 54 per cent. Although improvement may be noted in less than a week a maximum degree may not be achieved for many months when the patient has been hospitalized for a long time.

### Duration of Hospital Stay

The duration of the psychosis, as measured by the length of hospital stay, is an important factor in influencing the degree of clinical improvement. In the opinion of most investigators[24,26] the longer the duration, the less likely the possibilities of all grades of improvement, and this is seen most strikingly in the number of patients who are sent out of the hospital in a state of remission (no residual symptoms) or social recovery (slight residual symptoms). In the acute cases these two grades of improvement range between 43 per cent[17] and 79 per cent[22] whereas in the chronic stage of the psychosis, the values are decidedly lower, decreasing to 5 per cent[24] to 32 per cent.[26] Obviously, it would be necessary to maintain the treatment for a longer time in the chronic patients.

### Clinical Results

For the vast majority of investigators the administration of chlorpromazine and reserpine has produced definite behavioral improvement in the majority of schizophrenic patients. Violent, agitated, anxious, assaultive, denudative patients have, on the whole, shown a decrease in aggressive behavior, a lessened responsiveness to disturbing hallucinations and delusions and an increased degree of socialization with other patients, as well as with ward and medical personnel. This lessened emotional tension has allowed for more contact with the physician, the nurse and the occupational and industrial therapist. Granted this degree of improvement, which, from the point of view of the hospital administrator and of the patient, is quite important, the question arises how the number of patients being sent out to resume their normal degree of activity in the community compares with that obtained in patients under other methods of treatment. Even if the discharge rate is no more than with custodial care, electroshock, insulin coma or lobotomy treatments, the simplicity, economy and lesser emotional turmoil would make the drug treatment preferable so long as there were no high percentage of untoward effects.

Unfortunately, most of the figures for improvement obtained after drug treatment are cited as if the patients existed in a therapeutic vacuum. Disregarding for the moment the bias that therapists tend to assume toward a new method of therapy, the fact remains that in most well run mental hospitals a definite percentage of patients are discharged to the community in a condition approximating that observed before they became ill. For this I shall have to draw on figures obtained in Alexander's[28] review of the literature in 1953 (Table 1). In 11,080 schizophrenic patients with varying periods in the hospital complete and social recovery was obtained in 19 per cent. This figure is the base line against which all

other methods of therapy must be compared since it is invariably present. In 7357 schizophrenic patients treated with convulsive-shock therapy, the rate of complete and social recovery is 29 per cent. In 9483 cases of schizophrenia treated by the insulin-coma technic, the figure is 48 per cent. In 1211[30-32] patients treated with lobotomy, the value is 18 per cent. In 1517 cases that I have obtained from the literature, the figure is 34 per cent for chlorpromazine. For reserpine (897 cases) there is a corresponding figure of 22 per cent. The figures for lobotomy must be evaluated on the basis that this technic was a last resort in patients who had not improved by any other method of treatment.

TABLE 1. *Effects of Various Types of Therapies in Schizophrenic Patients.*

| TYPE OF THERAPY | NO. OF PATIENTS | COMPLETE REMISSION COMBINED WITH SOCIAL REMISSION |
|---|---|---|
| | | % |
| Custodial & supportive treatment* | 11,080 | 19 |
| Convulsive shock* | 7,357 | 29 |
| Insulin coma* | 9,483 | 48 |
| Lobotomy† | 1,211 | 18 |
| Chlorpromazine | 1,517 | 34 |
| Reserpine | 897 | 22 |

*Figures derived from Alexander.[28]
†Figures derived from Greenblatt et al.[29] Freeman & Watts,[30] Walker[31] and Great Britain Board of Control.[32]

It seems evident, then, that of all the forms of somatic therapy, insulin-coma treatment has the highest remission rate, and indeed Bleuler and Stoll[33] believe that this method brings a more lasting and basic psychotherapeutic accessibility than the drugs do. At any rate, two facts are evident: despite the widespread change in behavioral manifestations — that is, the "tranquilization" — the percentage of recovered cases with drugs is roughly comparable to that obtained by the shock treatments; and reserpine is not as effective as chlorpromazine in producing recoveries. The superiority of chlorpromazine over reserpine is further attested by a survey Margolis[34] recently made, in which 19 of 22 psychiatrists with extensive experience with the two drugs preferred chlorpromazine. He mentions that Azima, in a report of a recent international colloquium on chlorpromazine, notes the same over-all preference for this drug.

### Ideation Content

As has been mentioned, there is general agreement on the behavioral improvement in patients on these medications. There is less agreement about whether the intrinsic psychotic mechanisms have been affected. It could be safely assumed that in the patients sent home with complete or with social remissions there has been a reinstitution, to at least a marked degree, of the prepsychotic personality. In the other patients, who have lost their aggressive or hostile behavior, the disappearance of hallucinations and delusions, and the reconstitution of fragmented thinking is still in doubt. Some authors speak of a disappearance of these phenomena,[20-22,35] others of a lessening of their intensity,[15,19] and still others of no change in the ideational content.[18,36,37] This point, as yet, is unsettled, and it is probably safer to assume that in nonrecovered patients there is greater indifference to these phenomena. This feature, in itself, is of value since the lesser interaction of the patient to his disturbing ideational content may weaken the intensity of the emotional drive that tends to perpetuate the existence of the abnormal thought content.

### Subtypes

Of the various subtypes of schizophrenia, many authors have noted the superiority of results in the paranoid and catatonic over those of the hebephrenic patients. In many cases this is stated as a flat impression, but in some publications[21,22,24,27,38] a statistical breakdown is shown. I have been curious enough to compile some of these figures and offer these as a sample of moderate to marked degrees of improvement in the three subtypes with either drug (Table 2).

TABLE 2. *Effects of Chlorpromazine and Reserpine Therapy in Subtypes of Schizophrenia.*

| SUBTYPE | NO. OF PATIENTS | MARKED OR MODERATE IMPROVEMENT |
|---|---|---|
| | | % |
| Paranoid | 317 | 54 |
| Catatonic | 322 | 37 |
| Hebephrenic | 153 | 33 |

It is evident that the paranoid cases show the best results, with the catatonic next. However, the difference between the catatonic and hebephrenic types is probably of no significance. The result is interesting, though not definitive, since of the three categories one would have expected that the catatonic variety, with its impulsive outbursts, should show the greatest degree of change. On the other hand, it may be that the reason for the superiority in results of the paranoid group may lie in their relatively better integration and easier restoration to a normal level. One would have anticipated much poorer results in the hebephrenic group, but there may have been some selection here in that the most disturbed patients were chosen for treatment out of a larger sample of burnt-out and vegetating persons.

### Tolerance to Drugs

In the usual course of treatment the dose is increased to a maximal therapeutic level, depending on

the clinical course, and then gradually reduced. No tolerance to the medication, such as a need for increased dosage, is noted by the majority of authors during the course of treatment. This point is further strengthened by the fact that, as the patient improves, the dosage can be reduced while the clinical improvement is maintained. On the other hand, Sainz[21] has stated that a tolerance to chlorpromazine appears in all cases as shown by the fact that an increase in dosage of 20-50 per cent is needed between the second and third months of treatment to maintain the patient. Rees and Lambert[12] have found that even after the initial improvement has been achieved, relapses occurred under constant dosages of chlorpromazine in 78 of 117 cases of anxiety states. Neither investigator used high dosages, and this phenomenon might appear only when the dosage level was at a critical or threshold stage.

#### Relapse

A problem that is undergoing a good deal of discussion is that of the duration of treatment needed to prevent relapses. Approximately 33 per cent of all patients sent out of state hospitals under previous forms of therapy have had to return. What happens to the drug-treated patients? It is the general consensus that those with acute cases, after a prolonged tapering-off process, should be sent home without medication but that many of those with chronic cases, particularly those without striking improvement, should be kept on maintenance doses of 100 mg. of chlorpromazine or 2-3 mg. of reserpine. Barsa and Kline[24] state that in some patients on reserpine the therapeutic effect lasts only as long as the drug is administered. Pennington[39] notes that 20 per cent of the discharged patients treated with reserpine returned to the hospital, most of them because they stopped taking the drug. Freyhan[40] states that 32 per cent of the improved schizophrenic patients relapsed after termination of treatment, a third of them in less than a month. I have already mentioned the results of Rees and Lambert,[12] in whose improved patients 66 per cent relapsed despite continued treatment. On the other hand Goldman and Stephens[38] and Pollack[41] found that only 5-6 per cent of the chlorpromazine-treated patients discharged with medication had to return as compared with 30 per cent of those treated by other methods.

This problem can only be solved in the future. It is probably wisest to omit the medication in the cases of recent origin and continue it in the chronic or recurrent cases. So far as the individual episode is concerned retreatment after relapse usually results in the previously noted level of improvement, so that not too much is lost if the relapse occurs because of the discontinuance of the drug. Periodic observations of the patient must be made, however, to prevent or treat any of the complications.

### Manic-Depressive Psychosis

In manic attacks, general experience agrees that the drugs are very effective in diminishing the psychomotor agitation. Approximately a half to two thirds of the cases show excellent results. According to Goldman[26] the manic episode subsides as quickly as after electroshock treatment and even more rapidly according to Delay and Deniker.[14] There is an occasional dissenting note. Bennett[36] found no effect comparable with that obtained with electroshock. Sainz[21] states that in 17 patients there was a reduction in activity in all, but 4 went into a depressed phase and all relapsed after discontinuing medication. In general, however, manic excitement seems to be one of the most favorable states for the employment of the drugs.

The case is somewhat different for depressions. The vast majority of investigators[14,15,20,22,35,36] agree that the drugs are of little value and that electroshock treatment is the technic that should be used. When there is marked agitation with the depression this phase subsides, but the underlying psychomotor retardation remains. As a matter of fact, the depression may be intensified, especially by reserpine, since Hollister et al.[5] have noted in 7 normal subjects that 1 mg. daily caused a mild depression; Freis[42] described 5 cases of depression in patients with hypertension taking reserpine (2 with suicidal trends), and Gosline and Kline,[43] in 100 acute cases treated with reserpine, noted a 9 per cent incidence of depressions, half of which were suicidal. Margolis,[34] in a recent survey of the literature and of psychiatric practice, collected a total of 177 cases of depression that had been treated with reserpine. Undoubtedly, in many cases other factors besides the drug influenced the onset of the depressive state, but the number of cases is certainly large enough to warrant care in its use in depression-prone persons.

### Aged Patients

The aged now form approximately a third of the state-hospital admissions and present many problems from the point of view of confusion, restlessness, combativeness and irritability. In these cases dosages should be started at a low level, 10-25 mg. of chlorpromazine three times a day, rising to a possible maximum of 200 mg. or 1-3 mg. of reserpine daily. The published results have been in general good, half to three quarters showing a definite improvement in behavior, with the result that some can be sent home to their families on small maintenance dosages.[44-46] The results seem to be better when there is definite agitation, since Settel[44] reports improvement in 40 out of 48 with irritability and apprehension compared with a similar change in 22 out of 41 with depressive features. It is not to be expected that the cerebral changes will be affected by the medication, but the

improvement in behavior will make life easier for such fragile patients, their relatives and hospital personnel.

### Psychoneuroses

The results of treatment in the psychoneuroses is quite variable. In the anxiety states in which there is marked tension there is general agreement that about a half to two thirds of the patients[47-49] do well, although Bennett[36] found only a sedative effect in 5 out of 9 patients. Sabshin and Ramot[18] note only a moderate quieting effect in 20 per cent, and Kinross-Wright[30] says that although sleep, appetite and muscle tension improve, there is rarely a cure. The results seem to be more specific for the emotional tension than for reorientation of the patient's ideational content.

In hysteria, compulsive-obsessive neuroses, hypochondria and psychosomatic complaints the therapeutic effects have been in general poor, with occasional exceptions.[13,47,49] In cases characterized by depression the results are mixed.[48,49,51]

The dosages usually employed are 40 to 400 mg. of chlorpromazine or 1 to 2 mg. of reserpine. These dosages are small in comparison with those employed in the psychoses, but are limited because of the apparent lesser tolerance to the somnolent effects of the drugs in nonpsychotic patients.

### Mental Retardation

The drugs have also been of definite value in hyperactive, destructive, aggressive, mentally retarded patients of all ages.[38,52,53] In children the dosages have been 75 mg. of chlorpromazine or 1-2 mg. of reserpine. In adults the doses have been somewhat lower than the level used in schizophrenic psychoses. Approximately 50 per cent of them improve in behavior while the drug is maintained. In children the reduction in hyperkinetic behavior can result in an improvement in the intelligence quotient (owing to the diminution in distractibility).[52] Again, the treatment is symptomatic but at least has beneficial behavioral effects.

### Delirium

Acute delirious states associated with alcoholic intoxication respond favorably to either drug.[21,26,54,55] Initially, the drugs must be given parenterally in doses of 2.5-5.0 mg. of reserpine or 50 mg. of chlorpromazine, but when the patient quiets down, as he usually does within an hour, the other doses may be given orally. The patients are quiet, without the somnolence and confusion characterized by treatment with paraldehyde or the barbiturates. Although the acute stage is easily managed, Sainz[21] has found in 17 cases of chronic alcoholism that the administration of chlorpromazine relieved the anxiety but did not prevent the patients from drinking.

### Complications

Each drug has a long list of possible complications or side effects, but only a few are of any importance. Practically all are reversible with discontinuance of the medication, and some do not reappear on retreatment with the specific drug. So far as the complications are concerned, there is a factor of individual idiosyncrasy in most of them, although the influence of varying dosage cannot be discounted in some.

For chlorpromazine the side effects described are local tissue irritation (when injections are used), potentiation of effect of narcotics, sedatives or alcohol, sensitivity of aged or debilitated patients, constipation, galactorrhea, transient hyperthermia or hypothermia, dermatitis, confusion, convulsions, hypotension, jaundice, Parkinsonism and agranulocytosis. Only the last seven are of any importance, and only the last is dangerous. A toxic-confused state has occasionally been noted by Kinross-Wright[22] that calls for discontinuance of the drug. Dermatitis, which may be troublesome not only to patients but also to nurses — in as many as 10 per cent of those handling the material.[26] It is treated by ACTH or steroids but according to Margolis[34] does not necessitate interruption of therapy. The hypotension is orthostatic and can be minimized if the patient rests for an hour in bed after a dose. Jaundice occurs in a variable number of cases and has been reported in as many as 8.3 per cent.[56] The rate of jaundice with higher doses (500 mg. and up) is on an average 1.4 per cent, with lower doses less than 1 per cent.[56] The jaundice is a benign condition, but some investigators continue the therapy and find that it diminishes.[34] Others interrupt the treatment and reinstitute the drug and find that the jaundice does not recur. Convulsions have occurred in intensive chlorpromazine therapy[23] but can be readily avoided by reduction of dosage. Parkinsonism usually follows higher dosages. Some investigators, such as Goldman[20] and Kinross-Wright,[26] consider it desirable to arrive at this stage and merely utilize anti-Parkinsonian drugs. It is easily controlled by reduction in the dosage. In my opinion, there is no more rationale in considering this complication a necessary accompaniment of the therapy than considering the production of Cushing's disease a desirable component of steroid therapy. In addition the somnolence and inco-ordination that accompany this syndrome go beyond the unique tranquilizing effects of the drug and approach the effect of heavy barbiturate therapy. The most serious complication is agranulocytosis. This is rare, occurring in 1 out of 50,000 to 100,000 patients, but it cannot be lightly disregarded.

Reserpine has less serious untoward effects. These include drowsiness, fatigue, nasal congestion, diarrhea,

bradycardia, hypotension, increased salivation, edema, convulsions, confusion and the Parkinsonian syndrome. The last three indicate overdosage and require diminution of the drug. Barsa and Kline,[24] like Goldman,[20] do not consider the development of the Parkinsonian symptoms as necessitating a diminution of dosage, but continue with accessory drugs to combat this. The tendency to depression with reserpine has already been discussed.

### Combination of Drugs and Electroshock Therapy

A final point to be mentioned is the combination of the two drugs in cases not responding to either, or the combination of one of the drugs with shock therapy. One is in sympathy with the clinician who is hard pressed to produce improvements in patients, but at present there is no scientific evidence that a combination of the two drugs will do better than either one. Regarding the utilization of either one of the drugs with shock therapy or insulin therapy, the literature[34] has already shown a certain number of cases with serious complications and deaths in drug-shock combinations, and this method must be approached with great caution.

### Discussion

There is little question that the utilization of the tranquilizing drugs has resulted in a definite behavioral improvement in many patients exhibiting aggressive, hostile, antisocial trends. From this point of view there has been a mild revolution in mental institutions in the decreased use of shock therapies, in the activities of the patients and in the appearance of the wards. Unfortunately, there are no statistics as yet about the effect on the economy of the hospitals to validate this point.

There is no definite evidence that the drugs affect the ideational content of the psychoses or even of the psychoneuroses. They diminish the emotional expression of the abnormal thought content, but it is questionable whether the underlying psychic turmoil is affected. This lessening of emotional tension is of value in many cases, particularly in those of recent onset, in that it conserves physical and psychic energy and allows the patient to reorient himself to reality. On the other hand, a recent paper[57] describes 14 cases in which further psychotic deterioration or enhanced anxiety was produced by treatment with these drugs because the submissiveness that followed psychologically threatened the patients in whom activity was the sole means of expressing their emotional conflicts. In other words, in some patients, restraint by any method, chemical, electric or surgical, may be of more benefit to the hospital than to the person concerned.

It is at this point that one may mention the desirability of psychotherapy in association with the treatment. The drugs afford a unique opportunity for intensive psychotherapy of patients in whom such an approach was previously impossible. The practical question arises regarding how this additional therapeutic aid will be obtained in mental hospitals at present inadequately staffed.

Finally, I wish to make one further comment. The effectiveness in altering behavior beyond the factor of suggestion has been attested in chronic patients in the double-blind studies I have previously mentioned. There have been no similarly controlled studies in acute admissions. This would require a very large number of patients, in the thousands, because of the higher improvement rate than in that of chronic cases. Nevertheless, it is the only method by which the effects of these agents on number of remissions, number of relapses and duration of hospitalization and ideational content can be properly evaluated. It would have to be an elaborate program but one that would make possible an estimation of the true value of these drugs at least a decade before the usual trial-and-error methods determine their true place in treatment.

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# ACUTE ASEPTIC MYOCARDITIS AND MENINGOENCEPHALITIS IN THE NEWBORN CHILD INFECTED WITH COXSACKIE VIRUS GROUP B, TYPE 3*

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THIS paper presents evidence for intra-uterine infection with a Coxsackie virus Group B, Type 3, in an infant in whom acute myocarditis and meningoencephalitis developed. The infant was delivered by cesarean section and died seven days later. The virus was recovered post mortem from the thoracic spinal cord. The clinical history, along with pertinent pathological and virologic findings, is presented, with a discussion of their significance.

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## CASE REPORT

The patient's mother, a 37-year-old para III, gravida IV, was well until the 38th week of pregnancy, when an upper respiratory infection characterized by coryza, sneezing and malaise developed. The temperature was not noted. Two days later she passed a large amount of blood per vaginam and was brought to the Boston Lying-in Hospital, where the diagnosis of placenta praevia was made, and an immediate cesarean section performed. The mother made an uneventful recovery.

The infant, a female, weighed 3.7 kg. (8 pounds, 4 ounces) at birth. She breathed spontaneously, and her condition appeared good. Several hours after birth, however, a croupy cough when she was crying and an inspiratory crow developed, but she remained otherwise well until the 3d day, when the temperature, previously between 97 and 98°F. by rectum, rose to 100.2°F. She became lethargic and took feedings poorly. Significant findings on physical examination were limited to physiologic jaundice and pedal cyanosis. A red-cell count of 5,840,000 and a white-cell count of 25,000, with 49 per cent neutrophils and 51 per cent lymphocytes, were recorded. Materials for throat and blood cultures were

obtained, and therapy with penicillin, 25,000 units, and streptomycin, 75 mg. every 8 hours, was instituted. The throat culture later revealed nonhemolytic streptococci, and the blood culture was negative. On the next day the patient was afebrile. A chest film was interpreted as indicating bilateral atelectasis, with no evidence of pneumonitis. On the following day, the 5th day of life, fever recurred, and a lumbar puncture was performed, revealing clear, xanthochromic cerebrospinal fluid under a normal pressure, with a ++ Pandy reaction and a negative test for sugar, and containing 132 white cells per cubic millimeter, 95 per cent of which were mononuclear cells. Smear and culture showed no organisms. The infant was transferred to the Children's Medical Center, Boston, for further diagnosis and treatment.

On admission, she weighed 3.2 kg. (7 pounds, 2 ounces); she was active, and her cry was strong. The temperature was 101.4°F. by rectum, the pulse 150, and the respirations 35. Additional findings of significance included a moderate jaundice, a systolic murmur at the base of the heart and a liver edge palpable 2 cm. below the right costal margin. Urinalysis was not remarkable. A lumbar puncture at this time revealed 98 red cells and 132 white cells per cubic millimeter, with 90 per cent mononuclear cells. The total protein was 75 mg. per 100 ml., but the spinal-fluid sugar was within normal limits. Again, no organisms were seen on smear or culture. Hematologic examination showed a hemoglobin of 16.5 gm. per 100 ml. and a white-cell count of 31,200, with 40 per cent lymphocytes, 14 per cent neutrophils, 18 per cent band forms, 26 per cent metamyelocytes and 2 per cent monocytes. Treatment with penicillin and streptomycin was continued to which were added sulfadiazine and chloramphenicol. On the day of transfer fluids were administered intravenously, but on the following day the patient was given an evaporated-milk formula, which she took fairly well until shortly before death.

FIGURE 1. *Myocardium of the Left Ventricle, Showing Patchy Infiltration with Polymorphonuclear Leukocytes and Lymphocytes, with Focal Necrosis of the Myocardial Fibers (Hematoxylin and Eosin Stain X50).*

On the 6th day her condition abruptly grew worse. A lumbar puncture was again performed, and revealing 327 white cells per cubic millimeter (95 per cent mononuclear cells and 5 per cent neutrophils). The Pandy reaction was ++, but again the sugar was within normal limits and smears and cultures of the fluid revealed no microorganisms. The temperature fluctuated between 100 and 101°F. by rectum and the pulse rose to 160 and the respirations to 60, persisting at these levels until 1 hour before death, when they dropped abruptly. At 3:35 a.m. on the 7th day of life, the temperature was 94.6°F. by rectum, the pulse 120, and the respirations 30. Shortly thereafter the patient died.

A complete autopsy was performed 6 hours after death. The infant weighed 3.2 kg. (7 pounds) and measured 51 cm. in length. She was well developed and moderately icteric.

The heart weighed 29 gm. (expected weight, 18 gm.) and was firm on palpation. The pulmonic valve was bicuspid, 1 cusp measuring 1.6 cm. and the other 0.4 cm. After fixation in 10 per cent formalin solution *(USP)* the myocardium assumed a mottled appearance, yellowish areas alternating with brownish ones. This change was not apparent in the fresh state.

The lungs were moderately well aerated. Their parenchyma was markedly congested, and numerous petechial hemorrhages were present on the pleural surfaces as well as throughout the parenchyma. The liver protruded 4 or 5 cm. below the costal margin and weighed 180 gm. (expected weight, 96 gm.). This organ was otherwise unremarkable.

The brain weighed 352 gm. (expected weight, 358 gm.). Routine coronal sections after formalin fixation failed to reveal any abnormalities. The spinal cord was removed *in toto* by means of a new scalpel blade. No gross abnormalities were seen. A portion of the thoracic cord was then carefully removed, with precautions to avoid contamination, and stored at −20°C. Cultures of heart's blood and cerebrospinal fluid showed no growth on various bacteriologic mediums.

FIGURE 2. *Section of the Pons Cerebri, Showing Two Small Infiltrations by Polymorphonuclear Leukocytes, with Degeneration of Glial Tissue and Ganglion Cells (Hematoxylin and Eosin Stain X70).*

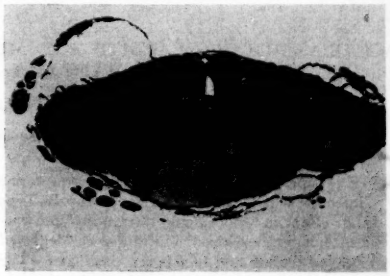

FIGURE 3. *Spinal Cord, Showing Focal Infiltration with Polymorphonuclear Leukocytes and Round Cells in the Region of the Reticular Formation and Adjacent Tissues (Hematoxylin and Eosin Stain X20).*

For microscopical examination portions of all major organs were fixed in both Zenker's fluid and 10 per cent formalin *(U.S.P.)*. Routine hematoxylin and eosin sections were prepared. In addition sections of the heart were examined with the use of the following special stains: periodic acid Schiff, toluidine blue eosin, phosphotungstic acid hematoxylin and Prussian blue.

In the heart a diffuse myocarditis was found that chiefly involved the portions near the annulus fibrosus and consisted of an infiltration with polymorphonuclear leukocytes, macro-

phages and occasional lymphocytes (Fig. 1). Numerous eosinophils and degenerating leukocytes were also present. In these confluent areas of inflammation there was degeneration of myocardial fibers and congestion of small vessels. The epicardium showed slight inflammatory-cell infiltration. Neither organisms nor inclusion bodies were seen.

In the brain and spinal cord the meninges revealed edema and a diffuse infiltration with moderate numbers of macrophages and occasional polymorphonuclear leukocytes. The veins were markedly congested. Two small foci of degeneration, with gitter-cell infiltration and a few polymorphonuclear leukocytes, were seen in sections of the cerebellum. Two similar areas of encephalitis were present in the tractus

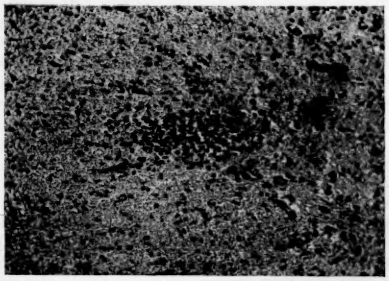

FIGURE 4. *Same Specimen As Figure 3, Showing Infiltration in Reticular Formation, with Degeneration of Fibers and of Occasional Ganglion Cells (Hematoxylin and Eosin Stain X140).*

corticospinalis of the pons (Fig. 2). Numerous sections of the spinal cord showed degenerative and inflammatory lesions in the lateral aspects of the anterior horns and in the reticular formations (Fig. 3 and 4); these were scattered throughout the length of the cord but were most frequent in the thoracic

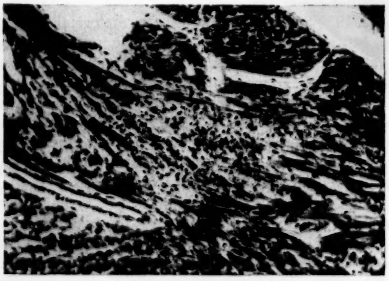

FIGURE 5. *Section of the Myocardium of a Mouse (Third Passage), Showing Myocardial Necrosis and Infiltration with Polymorphonuclear Leukocytes (Hematoxylin and Eosin Stain X70).*

portions. In these lesions macrophages and polymorphonuclear leukocytes had replaced normal cord substance, and occasional degenerated ganglion cells could be seen in these foci. There was no purulent meningitis. As in the heart no organisms or inclusion bodies were seen.

In addition, the pleura was edematous and contained foci of lymphocyte and macrophage infiltration. Small focal infiltrations of polymorphonuclear leukocytes were encountered in the pancreas, and small foci of inflammatory cells were seen in the central portions of the fetal adrenal cortex. Aside from the findings mentioned above, histologic examination was not remarkable, revealing only such changes as would be expected in congestive heart failure. The placenta was not examined pathologically.

The only specimen available for virologic study was the section of thoracic spinal cord carefully removed for this purpose. Attempts to isolate a virus were made with the use of roller-tube tissue cultures as routinely prepared and employed for such purposes in this laboratory.[3] Cultures of human renal tissue and human embryonic skin and muscle were inoculated with the supernatant fluid from a 10 per cent suspension of the spinal-cord tissue. A transmissible cytopathogenic agent was revealed in the culture of renal cells. A virus exhibiting the same properties was isolated from another preparation of the cord tissue. Both agents were subsequently identified as Coxsackie virus Group B, Type 3, in neutralization tests with specific antiserums. The cytopathogenic effect was not observed in the cultures of human embryonic skin and muscle. In cultures of human renal tissue, degeneration of all the cells did not occur, even after several serial passages of the agent.

Infected fluid from the renal-cell cultures produced no cytopathogenic effect in cultures of human embryonic skin and muscle, testis and human foreskin. A limited, slowly progressive effect was noted in cultures of human myometri-

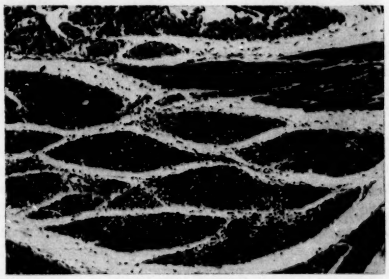

FIGURE 6. *Section through the Fat Pad of the Dorsum of the Neck of a Mouse (Third Passage), Showing Acute Fat Necrosis and Infiltration by Polymorphonuclear Leukocytes (Hematoxylin and Eosin Stain X70).*

um, and rapid and complete degeneration followed addition of the virus to cultures of trypsinized monkey-kidney cells. The infectivity titer of the virus propagated in monkey-kidney cells was $10^{6.5}$ $ID_{50}$ per milliliter.

No serum from the infant was available. A serum specimen obtained from the mother on January 10, 1954, 21 days post partum, when tested in roller-tube cultures of trypsinized monkey-kidney cells, was able to neutralize between 100 and 300 $ID_{50}$ of the recovered agent at an initial serum dilution of 1:80 but not at 1:160. A specimen of gamma globulin prepared in 1944, when similarly tested, delayed but did not prevent the appearance of a cytopathogenic effect when diluted at 1:8, the lowest dilution tested, and a pool of 34 serums prepared in 1950 from residents in this area showed no neutralizing antibodies at an initial dilution of 1:2. Evidence, however, that this agent has recently been responsible for other infections in this part of the country was provided by the demonstration of neutralizing antibodies at an initial titer of 1:32 but not at 1:128 in a pool of gamma globulin prepared from placentas collected at Eastern Seaboard hospitals early in 1954.

Four consecutive passages of the agent were made in 1-day-old suckling white mice, both intracerebral and subcutaneous routes of inoculation being used. For the 1st passage, infected tissue-culture fluid was used, and subsequently the supernatant fluid from 20 per cent brain and carcass suspensions. No specific signs of infection were noted until the 3d and 4th passages, when the mice became obviously ill and ataxic and lost weight, and their hind legs appeared weak. Of these, several were killed for microscopical ex-

amination. In addition a brain-and-carcass suspension was prepared from another, representing the 4th passage, and an aliquot of the supernatant fluid inoculated into roller-tube cultures of both human and monkey renal tissue. In both, the presence of a cytopathogenic agent was noted that was later also identified as Coxsackie virus Group B, Type 3.

The suckling mice killed for pathological examination were immediately fixed in Bouin's fluid, and routine hematoxylin and eosin sections were prepared.

From animals included in the 3d passage sections through the heart showed an acute myocarditis (Fig. 5), similar to that found in the patient. Additional sections revealed extensive necrosis and acute inflammation of the fat pads of the neck (Fig. 6). No other lesions were encountered.

The only lesion encountered in the mouse from the 4th passage was an acute inflammatory process, with degeneration, in the hippocampus, involving particularly the ganglion cells (Fig. 7).

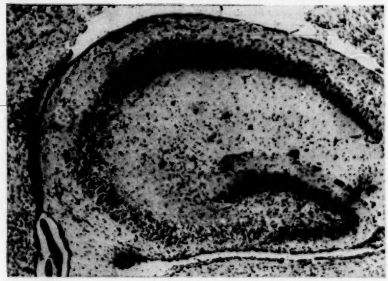

FIGURE 7. *Section through the Hippocampus of a Mouse (Fourth Passage), Showing Selective Acute Destruction of the Neurons of the Hippocampus, with Minimal Infiltration by Polymorphonuclear Leukocytes (Hematoxylin and Eosin Stain X55).*

Since the lesions in the mice were typical of those induced by Coxsackie viruses Group B this agent was submitted to Dr. Gilbert Dalldorf, director of Laboratories, State of New York, Department of Health, for further serologic identification. At his laboratories, tissue-culture neutralization tests, confirmed by neutralization tests in suckling mice, identified the agent as a Coxsackie virus Group B, Type 3. This identification was confirmed in our laboratory by tests on the agent with immune serums for the several Group B Coxsackie viruses supplied through the courtesy of Dr. Dalldorf.

## DISCUSSION

Myocarditis has been reported as occurring in association with a large variety of heterogenous disorders.[2,3] In certain cases, however, no disease is associated that appears to account for the myocardial lesions. Such cases have usually been considered to represent one form of primary myocardial disease and have been variously designated as interstitial, isolated, focal or idiopathic myocarditis. Saphir,[2,4] in reviewing this subject, states that this diagnosis should be made only in the absence of any other pathologic process that could be correlated with the myocardial involvement. He stresses, in addition, the absence of endocardial and pericardial lesions as a prerequisite for this diagnosis.

The rigidity of these criteria is questioned by Tedeschi and Stevenson,[5] who point out that in a number of the reported cases of this form of primary myocarditis a definite but less extensive involvement of the endocardium or epicardium has also been present, and in others evidence of concomitant or preceding infections of a minor nature.

The clinical and pathological features associated with this condition have been thoroughly reviewed.[2,5-7] In summary there is usually a relatively sudden onset, with anorexia, evidence of circulatory and respiratory embarrassment and tachycardia and with rapid progression to death or recovery. Slight fever is often present. Pathologically, examination of the myocardium reveals either a granulomatous process or an inflammatory infiltrate, which may be widespread but is usually patchy. In general the infiltrate consists of polymorphonuclear leukocytes, eosinophils, lymphocytes and macrophages.

Certain evidence indicates that at least some cases of this disease may be the manifestation of an infectious process usually not recognized as causally related to this entity. Pathologically, the lesions are identical with those seen in the myocarditis associated with certain acute infectious diseases. The fact that older infants and children appear to be affected with greater frequency than those under six months[7,8] also appears to be consistent with an infectious etiology since the first six months of life coincide approximately with the expected persistence of maternal antibodies. This condition has frequently been immediately preceded by or associated at the onset with signs of an upper respiratory infection, often culminating in an interstitial pneumonia.[5,9,10] In several cases, moreover, this disease has had an epidemic type of distribution.[8,11-13]

In 1952 Stoeber[8] reviewed the pathological findings in 140 autopsied cases of "epidemic myocarditis of infancy." This disease, relatively common between 1937 and 1944, according to the author, had an epidemic distribution in certain areas of Munich and in several cases involved siblings. Clinically, the cases were characterized by sudden loss of appetite, by vomiting and by cyanosis and dyspnea, little relieved by oxygen. Tachycardia and arrhythmias were frequent. Grippelike infections were occasionally also noted but with little fever. Hepatomegaly and occasionally splenomegaly were present. In a few of the patients convulsions occurred. Blood cultures revealed no bacteria. The illness was usually of short duration in those who survived, and the peak incidence was at about one year of age. Grossly, cardiac dilatation and some hypertrophy were seen, and bronchopneumonia, tracheobronchitis and hepatomegaly were frequent. Histological study of cardiac specimens from 68 patients revealed myocarditis of varying severity, unassociated with endocarditis and rarely with pericarditis. The spinal cords and brains were not examined as routine, but none of 4 brains included showed encephalitis. Photomicrographs of the cardiac lesions revealed myocarditis resembling the lesions in

our patient. Although infection with agents of the encephalomyocarditis group was one of the etiologic factors considered, experimental lesions produced by one of these agents in mice were not identical with those found in the children. Only one of three convalescent serums tested contained neutralizing antibodies for encephalomyocarditis virus. The possible role of Coxsackie virus was also suggested.

In 1953 an outbreak of illness involving several infants occurred in a newborn nursery in Victoria, Australia.[13] This illness was also characterized by anorexia, tachycardia, fever, cyanosis and, occasionally, diarrhea. Meningismus developed in a few infants. Several of the mothers had recently experienced nonspecific febrile or upper respiratory infections. Five of the infants died. At post-mortem examination pathological changes were found primarily in the hearts, which were enlarged, soft and friable. On microscopical examination diffuse myocarditis, with a predominantly round-cell infiltration, was found, along with some necrosis of muscle fibers. The brains were incompletely examined, and no sections of the spinal cord were made. Suckling mice were inoculated with brain, feces and heart-muscle suspensions from certain of the patients, but none showed apparent illness. In a few cases blind passages were made, but no agent was recovered. These cases resemble closely those described by Stoeber[8] and those recently reported from South Africa.[11,12]

In 1955 Montgomery and his associates[11] reported an outbreak of acute illness involving 3 infants and occurring the previous year in a maternity home in Southern Rhodesia. One of the infants died with convulsions as a terminal event. The other 2 recovered after a week. Among the prominent signs were fever, tachypnea, tachycardia and vomiting. Post-mortem examination in the fatal case revealed a focal myocarditis. The adrenal medulla was markedly congested and contained a few foci of inflammatory cells. Other organs examined, including the brain, showed only congestion or no remarkable changes. From the stools in the fatal case and of one of the surviving infants, a Coxsackie virus Group B, Type 4, was recovered by inoculation of newborn mice. This agent was prevalent in the region at the time and was also recovered from a number of patients with pleurodynia and meningoencephalitis.

In 1955 Javett and his associates[12] described a similar outbreak, which had occurred in Johannesburg in 1952. Of 10 babies affected, 6 died. Prominent features again included a sudden onset, fever, tachycardia, tachypnea and, in addition, cyanosis. Occasionally, the illness was biphasic, the early signs being followed by improvement and then by an exacerbation. The course was rapid, terminating either in circulatory collapse and death or in apparently complete recovery. Autopsies were performed in 5 of the 6 fatal cases, but histologic examinations were carried out in only 3. These showed myocarditis and also, in 1, a focus of encephalitis. Signs of a meningoencephalitis were also present in 1 of the surviving infants, as indicated by a bulging fontanel, pleocytosis and an increased total protein in the cerebrospinal fluid. No viral studies were made in this case.

Evidence for the presence of a Coxsackie virus Group B was obtained from the feces of 2 of the 4 infants who survived. In 1 the agent was identified as a Group B, Type 3, strain; in the other the virus was not actually recovered, but inoculation of suckling mice with the fecal suspension produced lesions characteristic of infection with these agents. Attempts at isolation were also performed with various tissues obtained post mortem from 2 of the 3 infants with myocardial lesions. In neither of these cases was a virus actually recovered, although brain suspensions from both patients induced lesions in suckling mice consistent with Coxsackie Group B infection. More recently, in a similar case from Transvaal, Coxsackie Group B virus was recovered from the myocardium post mortem, but the type of this agent was not identified.

The etiologic role of certain Coxsackie viruses in various human illnesses is now established. Various aspects of these agents, characterized by "their unusual pathogenicity for and lesions in suckling mice," have recently been reviewed by Dalldorf.[14] The Coxsackie viruses are further classified into two groups, A and B, based chiefly on differences in the histologic changes induced in mice, Group A strains producing a generalized myopathy whereas Group B strains produce focal muscle lesions along with lesions of the central nervous system, fat pads and other tissues. With certain Group B strains a patchy myocarditis has been noted both in suckling[15-17] and in adult mice.[18] This lesion has been specifically noted in infections with a Group B, Type 3, strain.[18,19] The present study, along with recent reports by Javett and his co-workers,[12] indicates that strains of Coxsackie virus Group B, Type 3, may produce a similar histologic appearance in man.

The evidence for various Group B Coxsackie strains, including Type 3, as etiologic agents in certain cases of aseptic meningitis and encephalitis is quite clear. Such agents not only have been found in frequent association with these conditions but also have been recovered from the cerebrospinal fluid of patients with these disorders[11,14,20] and in the present case from the thoracic spinal cord. There is now fairly unanimous agreement that pleurodynia is caused by these agents. In addition Group B viruses have been reported in association with a wide variety of clinical illness, including acute febrile illnesses, either uncomplicated or resembling influenza, infectious mononucleosis, sinusitis and appendicitis.[14,21,22] It is therefore quite probable that the infection experienced by the mother of our patient just before delivery represented one of the less specific manifestations of infection with a Coxsackie virus. Since Coxsackie viruses have on

occasion been recovered from the blood of both man[14] and experimentally infected primates[23] it is not unlikely that under certain conditions these agents cross the placental barrier. The delivery of this infant by cesarean section and the development of signs of illness shortly after birth, despite absence of further contact with the mother, clearly point to an intra-uterine infection. The finding of neutralizing antibodies for the agent in a blood specimen taken some three weeks after the mother's illness affords further support for this hypothesis.

Prenatal infections have been noted with the viruses of variola,[24,25] varicella,[26] measles[27] western equine encephalitis,[28] vaccinia[29] and poliomyelitis.[30,31] As far as we are aware this is the first case of such an infection with a Coxsackie virus and is also the first case in a human being with myocarditis from whose tissues Coxsackie virus of a specific type was isolated and identified.[32]

The clinical course in this infant followed the biphasic pattern noted by Javett and his associates[12] in a number of cases. The presence of cerebral, cerebellar, and spinal-cord lesions in this case, in addition to the myocarditis, is further evidence of the generalized nature and severity of the disease that can result from infection with at least one of the Coxsackie agents. It is of further interest that the same virus produced in suckling mice cerebral lesions and a myocarditis resembling that found in the patient.

Over the past several years, hitherto unrecognized viral agents have been recovered with increasing frequency, both from patients with a variety of specific and nonspecific clinical entities and from subjects who were presumably well. The greater number of these agents fall into one of three classifications, the Coxsackie viruses,[14] enteric cytopathogenic human orphan (ECHO) viruses[33] or the adenoidal-pharyngeal-conjunctival (APC) group.[34] The relation of many of these viruses to specific disease is still in doubt. The association, in man, of a myocarditis with an infection due to a Coxsackie virus and the frequent occurrence of minor respiratory infections and nonbacterial pneumonias in reported cases of myocarditis add weight to the hypothesis that many such cases may well be of viral etiology. Although minor and inapparent infections appear to be relatively common with many of the newly recognized viral agents, under special circumstances or in the predisposed person, some of these may be capable of producing severe or even fatal disease as in our case.

The apparent transplacental transmission of the agent in this case from a mother with a minor respiratory illness and the resultant fatal disease in the newborn infant are worthy of note. The possibility that a certain number of unexplained congenital anomalies are attributable to such unrecognized or minor infections with Coxsackie and other viral agents occurring during the first trimester of pregnancy deserves consideration.

It is evident from this discussion that certain cases of acute myocarditis not attributable to infection with larger micro-organisms are at present considered to represent a form of primary myocardial disease. Of these an undetermined proportion may be caused by viruses. The nomenclature for this condition is complex and confusing, ranging from terms descriptive of the pathologic process to "idiopathic." It is therefore suggested that such cases be given the nosologic designation "acute aseptic myocarditis" since the situation appears analogous to that previously existing in the terminology of certain acute meningitides and simplified by the widespread adoption of the designation "acute aseptic meningitis."

## Summary

The case history and pathological findings of a newborn infant infected *in utero* with Coxsackie virus Group B, Type 3, are presented. The infant died with a meningoencephalitis and acute myocarditis. The virus was recovered from the thoracic spinal cord. Evidence that this agent was responsible for the disease is presented.

We are indebted to Dr. John F. Enders for advice during the preparation of this paper, to Dr. Daniel Abramson for the post-partum serum and to Mr. John Carabitses for the photomicrographs.

Since this paper was submitted an additional account of fatal myocarditis due to Coxsackie virus Group B has appeared. The findings are presented in two reports.[35,36] From the heart muscle of each of 5 infants, one to three weeks of age, who died of myocarditis, a Group B virus was recovered. In 4 cases this was identified as Type B 4. A similar agent was isolated from the brain of 1 of these 4 patients.

Material from still another infant with fatal myocarditis was recently studied in our laboratory, and a Coxsackie virus Type B 4 recovered from the myocardium. This case will be described at a later date.

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# SOME OBSERVATIONS ON THE INCIDENCE OF THYROID CANCER IN THE UNITED STATES*

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THE present report is prompted by the absence in the medical literature of reliable data on the risk of papillary and nonpapillary cancer of the thyroid gland and on sex, age and geographic region as modifying factors of this risk.

Many articles have been published describing the occurrence of thyroid cancer. They are based on the records of individual hospitals or on the aggregate experience of several institutions. Authors interested in this subject have used clinical, surgical or autopsy observations as material for analysis. Indeed, it is hard to visualize how any study in the biology of a human disease could establish its roots anywhere but on well documented clinical histories. However, when these studies do not take into consideration the basic population served by the hospital in question, no valid conclusion can be reached on the frequency with which thyroid cancer occurs. Independent of the material used and of the variable degree of agreement existing in the conclusions reached by the different investigators, there is general uniformity in the pattern followed in expressing results.

Two sets of values usually characterize this pattern. In one, they are presented as a tabulation of the number of cases that fall in pre-established categories. In the second they are expressed as the ratios, usually percentile, of the number of cases in each category to the sum of the cases in the series, or to the total number of hospital admissions, or again to the number of patients with some other condition that the investigator believes might serve as a fruitful comparison or contrast. The information derived from knowing the absolute numbers in each category is obviously of little moment, since it indicates nothing beyond the self-evident fact that such cases do occur. The second set of values is more useful but only when one seeks to establish the relative numerical magnitude — that is, the relative frequency — with which two or more entities have occurred within the circumscribed experience of a particular institution. Often, however, this is not the purpose of communications of this sort: they usually aim at clarifying some aspects of the natural history of a disease and, in particular, how it is likely to manifest itself in the general population. Because various selective factors are involved in sorting out of the general population the patients who are eventually seen in a particular hospital, it is quite unwarranted to project to the general population conclusions based on what cannot be accepted as a representative sample. Even when the combined experience of several institutions is reported, one is rarely able to ascertain the basic population served by these hospitals.

By estimating the size of the population served by a number of large hospitals in different parts of the United States, Sokal[1] surmised that thyroid cancer occurs at an annual rate of 2.2 per 100,000 population. He apparently considered this was an overstatement because, in his words, "the institutions . . . are leading hospitals in their respective communities . . . [and also because] many of them are institutions where some special interest is taken in thyroid cancer." He seemed to believe that his earlier estimated

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incidence rate of 1.3 per 100,000 was a more correct one because it was based on "more comprehensive statistics of other types." The earlier estimate[2] was derived from the observation that in a collection of reports on a total of 22,000 cases of cancer, thyroid cancer accounted for 0.56 per cent. Apparently, this relative frequency was then applied to an estimated incidence rate for all forms of cancer combined. (Dorn[3] reported a total incidence rate of 230 per 100,000.) The data at Sokal's disposal did not permit estimates of the variation in the incidence of thyroid cancer by sex and age.

Alexander[4] obtained information on every case of thyroid cancer diagnosed in the hospitals of San Francisco during the period 1950-1954. He found that each year an average of 26 cases were diagnosed among the 800,000 residents of the city — an annual incidence of 3.3 per 100,000 population. Methodologically, Alexander's data should yield a better estimate than Sokal's, in that the cases seen in all the hospitals of a community can be related to the population in that community. However, these data may not be used for estimating the incidence of thyroid cancer in the United States because the experience in San Francisco may be unique. Furthermore, these data may yield an understatement because they are restricted to hospital cases.

The data on which the present report is based have been obtained and handled in a manner that permits a realistic approximation of the occurrence of thyroid cancer in the general population, and its variation with sex, age and geographic area. In addition, relative frequencies, as customarily appear in the literature, have been calculated to illustrate the inadvisability of using relative frequencies as an expression of risk.

## Method

The data used here were collected in 1947-1948 in the course of a survey conducted by the National Cancer Institute on morbidity from cancer in the United States.[5] Ten metropolitan areas were selected so that the proportionate distribution of their population among the three regions — North, South and West — was the same as that of all the cities with a population of 100,000 or more.* At the time of the study, the total population of these ten cities amounted to approximately 14,600,000 inhabitants, of whom 12,500,000 were white.

The survey method was designed to obtain reports on all or nearly all patients with cancer seen in hospitals, clinics and physicians' offices during a twelve-month period, 1947 or 1948. Senior medical students abstracted hospital and clinic records. A questionnaire was mailed to every physician in the area, and personal visits were made to physicians not responding. In addition the records of local vital-statistics offices were searched for information concerning deaths from cancer as a partial check on the completeness of reporting. It is believed that this method yielded information on practically every case of diagnosed cancer.

Cancer of the thyroid gland was reported to have been newly diagnosed in 336 persons who were residents of the ten cities surveyed in this study. Four out of every 5 diagnoses were microscopically confirmed. All reported cases were included in this analysis to ensure that the cases included were representative of all cases diagnosed in the population studied and to avoid understating the occurrence of thyroid cancer. A discussion of the epidemiologic method and the philosophy of defining a case of cancer is contained in the basic report on the morbidity survey.[5]

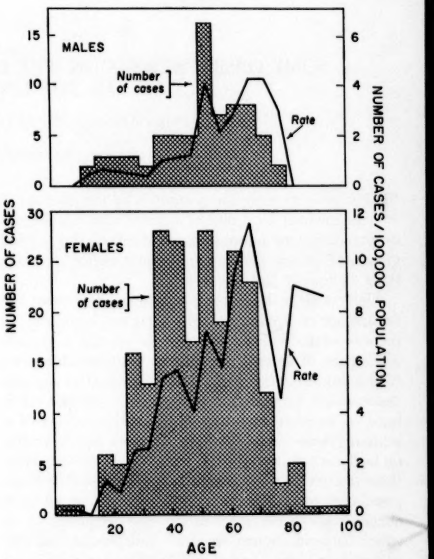


Figure 1. *Number of Newly Diagnosed Cases of Thyroid Cancer and Incidence Rates per 100,000 Population, by Sex and Age, among White Persons in Ten Urban Areas of the United States, 1947-48.*

*These data include all cases reported from hospitals and by private physicians, and cases obtained from death certificates.*

Only 30 cases occurred in the nonwhite population, and the small number involved precludes here a satisfactory analysis of the age distribution and incidence. However, it may be mentioned in passing that the majority of these cases occurred in women.

*The ten areas were as follows: Chicago, Dallas, Philadelphia and Pittsburgh in the North; Atlanta, Birmingham, Dallas and New Orleans in the South; and Denver and San Francisco, with Alameda County, in the West.

### Variation in Incidence by Sex and Age

Of the 306 cases in the white population, 74 occurred in males and 232 in females. The age distribution of these cases is graphically represented by the solid columns in Figure 1, which represent the number of cancers newly diagnosed during one calendar year according to the age of the patient at diagnosis. The columns serve to portray the relative contribution made by each age group of patients to the total number of newly diagnosed cancers. This is the only type of descriptive exposition attainable through hospital material. From these data alone, one could merely state that the consolidated clinical experience of ten metropolitan areas indicates, for example, that the absolute numbers of newly diagnosed thyroid cancers in the white female are approximately the same for the age groups between thirty-five and seventy, and that afterward they sharply decrease. One should at this point avoid the temptation of interpreting the dwindling number of cases newly diagnosed after the age of seventy as an indication that aging lessens the susceptibility to this neoplasm; otherwise, one would be coloring relative-frequency data with a concept of risk that they do not possess.

To translate these absolute figures of observed thyroid cancer in terms of the risk that the older age groups (and, for that matter, the whole of the general population) are exposed to, it is necessary to visualize each age-specific cancer figure in the perspective of the portion of the total population belonging to the same age group. In other words, using for each age group considered the number of newly diagnosed cancers as the numerator of a fraction, and for its denominator the number of persons in the population, an age-specific incidence rate is obtained that is then a true measure of the risk at that particular age. Usually, incidence rates are expressed in terms of number of new cases per 100,000 persons per year, and this custom has been followed in Table 1.

Table 1. *Annual Incidence of Thyroid Cancer by Race, Age and Sex in Ten Urban Areas in the United States, 1947-48.*

| Age | Both Sexes | | Males | | Females | |
|---|---|---|---|---|---|---|
| | white | nonwhite | white | nonwhite | white | nonwhite |
| *yr.* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* |
| All ages: | | | | | | |
| Crude rate | 2.5 | 1.5 | 1.2 | 0.1 | 3.7 | 2.8 |
| Age-adjusted rate* | 2.3 | 1.8 | 1.2 | 0.2 | 3.4 | 3.3 |
| 0-4 | 0.1 | 0 | 0 | 0 | 0.2 | 0 |
| 5-9 | 0.1 | 0 | 0 | 0 | 0.2 | 0 |
| 10-14 | 0.3 | 0 | 0.5 | 0 | 0 | 0 |
| 15-19 | 1.1 | 0 | 0.7 | 0 | 1.4 | 0 |
| 20-24 | 0.8 | 0 | 0.6 | 0 | 0.9 | 0 |
| 25-29 | 1.6 | 0.5 | 0.5 | 0 | 2.6 | 1.0 |
| 30-34 | 1.5 | 0.6 | 0.4 | 0 | 2.6 | 1.0 |
| 35-39 | 3.3 | 1.6 | 1.0 | 0 | 5.4 | 3.1 |
| 40-44 | 3.4 | 5.2 | 1.1 | 0 | 5.7 | 10.3 |
| 45-49 | 2.5 | 1.5 | 1.2 | 0 | 4.0 | 3.0 |
| 50-54 | 5.6 | 2.9 | 4.0 | 0 | 7.2 | 6.1 |
| 55-59 | 3.8 | 4.2 | 2.1 | 0 | 5.8 | 8.8 |
| 60-64 | 6.3 | 2.0 | 2.9 | 0 | 9.7 | 4.2 |
| 65-69 | 8.0 | 13.9 | 4.2 | 4.9 | 11.4 | 22.0 |
| 70-74 | 8.2 | 4.5 | 4.2 | 0 | 7.8 | 8.4 |
| 75-79 | 3.9 | 8.1 | 3.0 | 0 | 4.5 | 14.6 |
| 80-84 | 5.4 | 0 | 0 | 0 | 9.0 | 0 |
| 85 & over | 5.5 | 0 | 0 | 0 | 8.6 | 0 |

*Adjusted for age using 1950 United States population as standard.

It was mentioned previously that in both the white and nonwhite United States populations sampled in this study thyroid cancer preferentially selects women. The figures indicating this differential risk for each sex, by age and race (Table 1), are self-explanatory except perhaps for two sets of data that deserve some comment. These are the crude and the adjusted rates for all ages combined. The first ones are calculated by dividing the total number of cases observed in all age groups of a given category by the total number of individuals that make up that particular category. The result is then expressed in terms of 100,000 population. Differences may exist in the age distribution of otherwise numerically equal populations, and since

the risk of developing cancer is modified by age, the over-representation or under-representation of a particular age group will affect the total number of observed cancers. In other words crude rates do not take into account the relative distribution of age groups and, consequently, the age-specific risks within the total population. Thus, they cannot be safely compared to each other. In fact, from the crude rates of Table 1, one would be tempted to infer that white women are more susceptible to cancer than their nonwhite counterparts. The difficulty inherent in variations in the age distribution of different populations can be avoided by weighting the age-specific incidence rates for each population by the age distribution of a "standard population." In this study of newly diagnosed neoplasms to decrease with age. The relatively small number of cases found late in life may be ascribed in part to the smaller number of people in the older age groups and in part to the moderately decreased incidence at ages over seventy as compared with the previous decade. For instance, the number of cases observed after the age of seventy-five is very small, only 4 new cases being diagnosed in the age group eighty to eighty-four. However, the observed incidence of 9 per 100,000 represents a ninefold increase over that of the age group from twenty to twenty-five years, in which 5 new cases were diagnosed. Thus, although the ratio of the number of cases is approximately 1:1, the ratio of the incidence rates is 9:1.

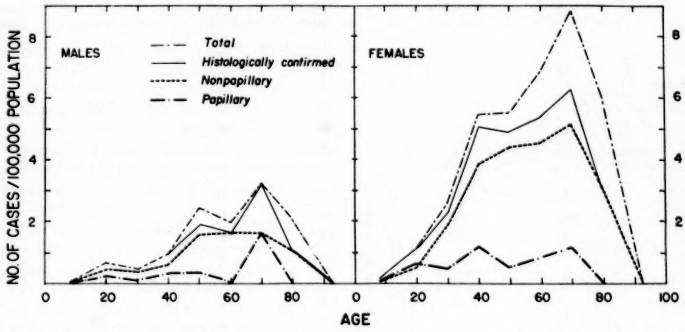


FIGURE 2. *Annual Incidence of Thyroid Cancer, by Sex and Age (All Reported Cases and Microscopically Confirmed Cases by Histologic Type among White Persons in Ten Urban Areas of the United States, 1947-48). Cases obtained from death certificates are excluded.*

the age distribution of the total United States population in 1950 was used as a standard. When the adjustment is made, it is seen that the risk of thyroid cancer is the same for the white and nonwhite women sampled in this study.

So far as the white population is concerned the incidence at different ages and for both sexes in Figure 1 is given the graphic representation of a solid line. This means that, on the basis of the experience in the ten survey areas, the corresponding point of the curve indicates how many *new* cases were diagnosed during one calendar year per 100,000 individuals belonging to each age group. The greater risk to which women are exposed can be readily appreciated. In white women, from the age of about fifteen or over, the risk increases progressively with age, whereas in white males it does not substantially increase until after the age of fifty. In both sexes the older age groups show a greater susceptibility than their younger counterparts.

It is important to recognize that risk increases with age in spite of the tendency for the absolute number

## VARIATION IN INCIDENCE BY HISTOLOGIC TYPE

An intriguing finding results if the total risk of cancer of the thyroid is apportioned between its papillary and nonpapillary variants. A specific histologic classification was known in 243 of the 306 neoplasms diagnosed in the white population. It was considered desirable to regard the papillary adenocarcinomas as a single entity and to group together all the nonpapillary adenocarcinomas. Among the males 13 cancers were papillary, and 43 nonpapillary in type. Among the female population 37 were papillary, and 150 nonpapillary. In the two sexes data on age-specific incidence were calculated for each histologic group and for both groups combined. These rates were used to establish the curve shown in Figure 2.

The shapes of the curves obtained with the use of Alexander's[4] figures for both sexes combined are in keeping with these results. It was of considerable interest to find that aging does not seem to affect the risk of papillary adenocarcinoma as unequivocally

as it influences the risk for the other histologic types. It appears as though the nonpapillary varieties are entirely responsible for the increasing incidence in the older age groups.

The frequency with which nodules occur in the thyroid gland has been reported to increase as age advances.[6,7] These observations tend to bring to mind the possibility that advancing age, thyroid nodularities and nonpapillary cancer may be interrelated. However, one should account for certain peculiarities in the geographic variations of cancer.

## Variations in Incidence by Geographic Regions

If the ten metropolitan areas are grouped according to their respective geographic region, and each regional group is considered as a unit, it is of great interest that during the survey year, the highest incidence of thyroid cancer occurred in the West (Table 2). The small numbers used in the computation of rates for Southern males probably afford too little statistical stability to justify broad generalizations. However, the figures for the Northern and Southern women appear substantial enough to warrant some comment. The incidence of thyroid cancer is the same in Northern and Southern women when adjustment is made for difference in the age distribution of the population. The equally frequent occurrence of cancer in two geographic regions otherwise so dissimilar in their experience with endemic goiter is a noteworthy finding. If future studies confirm this observation it may become necessary to discount the importance of endemic goiter as a major factor of etiologic significance.

It is unknown to what extent the observed differences among the ten urban areas might reflect differences in alertness to the possibility of thyroid cancer. Again, if confirmed by further investigation, this particular susceptibility to thyroid cancer of a population in whom goiters are not particularly common and whose members to a large extent live on the seacoast would be an epidemiologic observation hard to reconcile with the hypothesis that incriminates goiter as a precursor of thyroid cancer.

To conclude, it can be said that, as judged from the experience of the population of ten selected metropolitan areas, thyroid cancer occurs more frequently than is generally realized or conceded. This study has confirmed the observation that women are preferentially selected by this neoplasm and has also indicated that both white and nonwhite women share in the same risk. Furthermore, the analyzed material has suggested the presence of regional variation in its incidence as well as the possibility that a different risk operates for its papillary and nonpapillary varieties.

Table 2. *Age-Adjusted* Incidence Rates for Thyroid Cancer in Ten Urban Areas of the United States, by Region, Race and Sex, 1947-48.*

| Region | All Persons | Whites | | | Nonwhites | | |
|---|---|---|---|---|---|---|---|
| | | both sexes | males | females | both sexes | males | females |
| | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* | *per 100,000 population* |
| North | 2.0 | 2.1 | 1.2 | 2.9 | 1.7 | 0.0 | 3.4 |
| South | 1.5 | 1.6 | 0.1 | 2.9 | 1.3 | 0.5 | 2.0 |
| West | 4.0 | 4.1 | 1.6 | 6.4 | — | -- | — |

*Adjusted for age using 1950 United States population as standard.

## Summary and Conclusions

Relative frequency data as customarily published in the medical literature fail to measure risk.

Incidence rates are a much more realistic index of risk. They can be calculated only when the base population providing the cases under study can be defined.

Incidence rates for thyroid cancer by race, sex, age and geographic region are presented. These were calculated from the combined experience in thyroid cancer of ten metropolitan United States areas with a total population of 14,600,000 inhabitants.

White and nonwhite women share the same risk of thyroid cancer.

In both races women are preferentially selected over males.

Aging favors the development of thyroid cancer especially in its nonpapillary variants whereas the risk for papillary adenocarcinoma is not materially affected by age.

A comparison of the age-adjusted incidence rates for the three geographic regions indicates that during the study period the risk of thyroid cancer was highest in the West.

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# HYPERTENSIVE VASCULAR DISEASE IN ADOLESCENCE*

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A MEDICAL clinic devoted to the care of adolescents affords an excellent opportunity to further knowledge of the natural history of hypertensive vascular disease. This report presents case material indicating that the presence of a persistently elevated blood pressure in an adolescent boy or girl is deserving of further study, whether or not there are accompanying symptoms. On the basis of experience in this clinic, we believe that a careful blood-pressure determination is an important part of the adolescent's examination.

Elevation in blood pressure beyond the normal range in adolescence is not common. Various studies[1-6] suggest that the normal range of systolic blood pressure in adolescent boys is from 70 to 125 mm. and that in adolescent girls from 90 to 130 mm., and that the normal range of diastolic blood pressure for boys is from 45 to 85 mm. and that for girls from 50 to 85 mm. It seems to us, however, that Pickering's[1] statement, "the practice of making a sharp division between normal and pathologically high pressure is entirely arbitrary and is in the nature of an artefact," represents the most tenable point of view. We prefer to exercise such clinical judgment as we have in each case, setting only as a tentative range blood pressures above 90 mm. (diastolic) and 140 mm. (systolic) as worthy of careful investigation. McCrory and Nash[7] believe that when hypertension is found in young people it is almost invariably secondary to some renal, cardiovascular or endocrine disorder and that essential hypertension is rare.

During the three-year period 1952-1954, 1795 new patients were seen in the Adolescent Unit. A complete medical history is taken from both the parent and patient; routine study includes a thorough physical examination, photofluorogram of the chest, complete blood count, urinalysis, sedimentation rate and blood Hinton test. Further laboratory studies and clinical examinations are carried out when indicated.

In this group of 1795, 1.4 per cent (17 males and 8 females) had blood pressures that on two or more separate careful determinations were 140 systolic, 90 diastolic, or higher (Table 1). Seven of these patients (6 males and 1 female) had organic disease that accounted for their elevated blood pressure: 3 had coarctation of the aorta; 3 had glomerulonephritis; and 1 had unilateral thrombosis of the renal artery. The 18 others were considered to have a labile type of hypertension. Within the same interval one of us (W.T.G.) cared for a patient in his private practice who had benign essential hypertension.

Patients were considered to have a labile type of hypertension when, although the initial blood pressure equaled or exceeded 140 systolic, 90 diastolic, the majority of subsequent determinations were lower. When this diagnosis is made, normal blood-pressure readings should be the rule, and an occasional elevated blood pressure the exception. This is in contrast to the readings in organic disease or in essential hypertension, which are consistently higher than the normal range. It should be noted that the majority of tense, anxious adolescents who sought this clinic's help did *not* have elevated blood pressures at the time of the initial examination. Apparently, anxiety per se does not inevitably produce even this labile type of hypertension. Only long-term studies will reveal whether or not elevated blood pressure of the labile type indicates a prehypertensive state.[8-10]

The case report of a patient believed to have essential hypertension and seen elsewhere by one of us (W.T.G.) has been included in this paper.

TABLE 1. *Hypertension* among 1795 Consecutive Boys and Girls (Ranging from Twelve to Twenty-one Years of Age) Who Applied to an Outpatient Department over a Three-Year Period for Advice and Treatment Regarding a Variety of Conditions.*

| AGE | NO. OF CASES | | | ELEVATED BLOOD PRESSURE | | |
|---|---|---|---|---|---|---|
| | BOYS | GIRLS | TOTALS | BOYS | GIRLS | TOTALS |
| yr. | | | | | | |
| 12 | 285 | 153 | 438 | 2 | 3 | 5 |
| 13 | 222 | 141 | 363 | 8 | 2 | 10 |
| 14 | 197 | 123 | 320 | 2 | 0 | 2 |
| 15 | 125 | 109 | 234 | 1 | 0 | 1 |
| 16 | 123 | 83 | 206 | 1 | 1 | 2 |
| 17 | 79 | 42 | 121 | 2 | 2 | 4 |
| 18 | 41 | 27 | 68 | 0 | 0 | 0 |
| 19 | 14 | 12 | 26 | 1 | 0 | 1 |
| 20 | 10 | 7 | 17 | 0 | 0 | 0 |
| 21 | 1 | 1 | 2 | 0 | 0 | 0 |
| Totals | 1097 | 698 | 1795 | 17(1.6%) | 8(1.1%) | 25(1.4%) |

*Blood pressure of 140/90 or higher.

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## Case Reports

Case 1. At the age of 13 Billy's family physician found him to have a blood pressure of 150/90. The boy's complaint was intermittent severe headache since the age of 18 months. From this time and until he was 2 years of age Billy often held his head and cried; his mother was certain that he cried because of headaches. When he grew older and was able to describe his symptoms better, he said that his headache started in the frontal region, spreading to the left side of the head, and settled in the back of the neck. He would have severe headaches daily, followed by a free interval for a few weeks. The headaches lasted for 5 to 30 minutes. They were not preceded by an aura, nor accompanied by nausea, vomiting or blurred vision. On rare occasions he experienced dizziness, but never became unconscious.

There was no history suggestive of cardiorenal or endocrine disease in either the patient or his family. Before coming to the Unit he had had a complete neurologic examination, which was negative, and an electroencephalogram, which was normal.

At his 1st visit Billy appeared to be a healthy and well adjusted boy of 13. On physical examination his heart was not enlarged to percussion. There was a Grade 2 systolic murmur, best heard in the posterior aspect of the thorax. The pulmonic 2d sound was greater than the aortic. The blood pressure (in the supine position) was 138/88 to 140/90 in the right and 132/80 to 138/86 in the left arm. Femoral pulsations were absent, and the blood pressure in each leg was 90/0. The blood count and sedimentation rate were normal, and urinalysis and blood Hinton test negative.

Radiographic examination of the heart showed a slight increase in the transverse diameter, with a tortuous and prominent ascending aorta. The aortic arch was on the left; there was dentation of the esophagus below this level, and there was notching of the posterior end of the 6th left rib.

Since the clinical and x-ray findings were compatible with the diagnosis of coarctation of the aorta, surgery was performed. The blood pressure is now about 115/75 in the upper extremities. Femoral pulsations are present, and the blood pressure in the lower extremities is about 100/60. The headaches are no longer present.

Case 2. Three weeks before her 1st visit to the Unit, at the age of 13, Sally contracted a common cold. At that time her physician found hypertension, albuminuria and a heart murmur and suggested a complete diagnostic study.

The blood pressure had been normal when taken 2 years previously. She did not have a history of severe sore throats, gross hematuria or smoky urine; she denied excessive sweating, palpitation, faintness and dizziness. She had had several minor nosebleeds in the previous 2 years and a severe one coincident with her 1st menstrual period at the age of 12. There was a history of headaches, which had become more frequent during the 3 months before admission.

When she was 7 years old tuberculosis of the right knee developed. A fusion of the knee resulted in a cure of this disorder before her 9th birthday.

Physical examination revealed a healthy-appearing girl of average maturity. On ophthalmoscopic examination the fundi were normal. The heart was not enlarged. The 2d heart sound was accentuated and split, and there was a Grade 2, moderately rough systolic murmur best heard at the 2d left interspace and transmitted to the apex, neck and back. The blood pressure (in the supine position) was 210/140 in each arm and in each leg.

The complete blood count was normal. Urinalysis showed no albumin in the specimens collected during a period of bed rest, but in those collected after she had been up and about there was a + + to + + + test for albumin. There were no red blood cells in the centrifuged specimen. An electrocardiogram indicated hypertrophy of the left ventricle. The cardiac fluoroscopy was negative. An intravenous pyelogram and retrograde pyelogram were normal.

Blood-pressure readings of about 165/130 were obtained during sleep (both natural and after sedation). The change in blood pressure after Regitine was not significant. During a 5-day period of rest in the hospital the systolic pressure ranged from 160 to 210, and the diastolic from 100 to 145.

A split renal-function test showed the renal plasma flow to be 25 per cent less on the right side than on the left. An aortogram revealed a normal blood flow to the left kidney and normal renal arteries and kidney on the left. However, on the right side no major vessels could be visualized in the hilar area of the kidneys.

On the basis of these findings, it appeared that the hypertension was secondary to a renal anomaly. Surgical exploration was advised. The right kidney was atrophic, and there was thrombosis (not of recent origin) of the renal arteries. Nephrectomy on the right was done. The pathologist reported that the artery that should have supplied the upper pole of the kidney was thrombosed and that this area showed ischemic necrosis. The findings were compatible with the Goldblatt[11,12] kidney of experimental hypertension.

After nephrectomy the blood pressure fell to 160/100, where it has remained. Apparently, there is arteriolar disease in the remaining kidney.

Case 3. Three months before being seen in the Unit at 17 years of age, Joan was taken to her family physician because of eye fatigue. She had been examined by a specialist 2 years previously for the same complaint, and at that time was told that she did not need glasses. However, on this examination, the physician noted tachycardia and some elevation of blood pressure. He advised her to stop all exercise, and is said to have told her that if she had been 50 years old, he would have advised a 2-year period of bed rest.

Joan refused to return to this physician. However, she did not exercise during the remainder of the summer. When she returned to school in the fall the school nurse excluded her from physical-education courses. This upset Joan since she had hoped to make a career of physical education. She was referred to us for a further evaluation of the hypertension and tachycardia.

The past medical history was noncontributory, and there were no symptoms referable to the cardiovascular system except palpitation. She said that her heart beat rapidly if she had to talk in front of a group or when she went to a doctor. She said that she had always been very active and proficient in sports in school and had been very upset by the thought that heart disease might thwart her ambition to be a physical-education teacher.

During the physical examination this strong, healthy girl was extremely apprehensive and tense. There was a Grade 1 systolic murmur, which was soft and not transmitted, a blood pressure of 150/90, and a heart rate of 112. After an exercise-tolerance test[13] the blood pressure remained elevated. An electrocardiogram showed only sinus tachycardia; there was no conduction defect.

It was believed that this patient had a labile blood pressure. It was thought that her reaction to growing up, as well as her ambition to be more like her athletic father, were producing her basic anxiety. To observe both the patient and her blood pressure more thoroughly and to allow her to talk about some of the matters and feelings that confused her, she was seen by her physician 8 times during the subsequent 2 months. She was allowed to return to a full exercise program 1 month after her 1st visit. The blood pressure was still moderately elevated during the early visits, but it soon dropped to 120/70, and the tachycardia disappeared.

Case 4. Peter, a 21-year-old college student, said that he had noted increasing intolerance to cold and coldness of the hands and feet since 6 years of age. His general health had been excellent, and he had been supporting himself and earning his way through college by concurrently holding down a full-time job. However, during the winter months, he found it hard to concentrate on his studies because of coldness of the hands and feet, which at times were painful. Despite considerable discomfort, this symptom did not stop him from strenuous participation in such activities as skating and bicycle riding. He had occasional headaches on awaking in the morning, but these usually disappeared after breakfast and were never severe. Otherwise, the past history and review of the systems were irrelevant, and there was no family history of hypertensive, cardiovascular or glandular disease.

Physical examination showed a thin, but very well developed, tense, pleasant young man. The hands and feet were extremely cold but of excellent color and without cyanosis. The skin was dry and the hair coarse. There was no palpable abnormality of the thyroid gland. The blood pres-

sure was 155/95, and this reading persisted after rest. The heart and respiratory rates were 68 and 16 respectively, and the vital capacity was normal.

There were no signs of peripheral, hepatic, pulmonary or cerebral venous circulatory congestion. The heart was not enlarged, but the apical impulse was somewhat more forceful than usual, and there was a loud apical 1st heart sound and accentuated reduplicated aortic 2d sound. The apical 3d heart sound was normal. A Grade 1 systolic murmur was heard along the left sternal border. The peripheral pulses were normal throughout. The popliteal blood pressure was 170/100.

An electrocardiogram showed slight hypertrophy of the left ventricle, with extremely tall T waves and an R wave of 40 mm. in Lead $V_5$. A roentgenogram of the chest was normal. A complete blood count was normal, and urinalysis was negative. The basal metabolism rate was + 1 per cent. The serum cholesterol was 200 mg. per 100 ml., the uptake of radioactive iodine was 29 per cent in 24 hours, and the protein-bound iodine was 6.6 microgm. per 100 ml.

The patient was given reserpine (Serpasil), 0.25 mg. a day, for 2 weeks. Complete relief of the peripheral vasospasm and of the cold intolerance of the hands and feet followed. He also became less tense and was better able to concentrate on his studies. His appetite increased, and he gained 2.3 kg. (5 pounds) in weight. After 2 weeks, the reserpine dosage was reduced to 0.12 mg. a day because of sleepiness and fatigue. Two months after this medication was started, the blood pressure was 140/80, and the feet were warm and had excellent peripheral pulses.

Reserpine, 0.12 mg. every other day, was continued. Nine months later he continued to feel entirely well and free of all symptoms of cold intolerance. He completed a strenuous final year in college and is working as an electronic technician. His mild essential hypertension merits continued observation.

## Discussion

Despite the low incidence of hypertension in the adolescent age group, the importance of determining the blood pressure and of carefully evaluating an abnormal finding cannot be overemphasized. To omit to take an adolescent's blood pressure either because it is so rarely abnormal or because one believes that a high reading is likely to be caused by anxiety is to lose opportunities to suggest methods of treatment that could materially benefit, or even protect, the patient's life.

The 7 patients in this small series who were found to have one or another variety of organic disease obviously were entitled to an early recognition of their underlying disorder. No less deserving of attention were the 18 others in whom no structural abnormality could be found, but in whom an underlying anxiety might constitute a hazard to their future well-being. Any physical finding or any symptom that brings an adolescent to a physician gives him an opportunity to improve that young person's adjustment, emotional development and fitness for adult living.

Case 1 indicates the importance of palpation of the femoral arteries, Case 2 that of taking the blood pressure and of following up an abnormal finding with a thorough diagnostic study, and Case 3 the importance both of understanding and relieving an adolescent's source of emotional conflict and anxiety and of avoiding, except after careful consideration, the prescription of rest and restriction from activity — the latter are foreign to the normal adolescent's nature and are therefore more likely to aggravate than to improve his difficulties. Case 4, that of essential hypertension, is included to emphasize its rarity and as a reminder that it does occur in this age group. This diagnosis should not be made unless adequate clinical and laboratory investigation eliminates other physical and emotional disorders that affect the blood pressure.

The management and treatment of such conditions as coarctation of the aorta present little that is not understood. However, the early recognition, the differential diagnosis, the management and the natural history of what is now called labile hypertension are matters about which more needs to be known. Perhaps a better term than labile hypertension would be *labile circulatory system,* which would obviate the possibility of causing the anxiety that the word hypertension so frequently incites. Be this as it may, by routine blood-pressure determinations of adolescents, this and other conditions will be recognized earlier and more frequently. When recognized, the sources of adolescents' anxieties[14,15] should be kept in mind, and attention given to them. Only from long-term studies can one hope to learn whether the labile hypertension of adolescence is related to the hypertension of adulthood.

## Summary

In a series of 1795 adolescents 1.4 per cent (25) were found to have a blood pressure of at least 140 systolic, 90 diastolic.

Seven of these 25 had some organic disease; the others were considered to have labile hypertension.

Concurrently, a twenty-one-year-old man (seen in private practice) showed the features of benign essential hypertension.

Case reports of adolescents who had hypertension and who were found to have coarctation of the aorta, anomaly of the renal vessels, essential hypertension and labile hypertension are presented.

The importance of including the determination of the blood pressure in the medical examination of adolescents is emphasized, as is the need to recognize and give attention to the emotional conflicts and anxieties that are at times evidenced by labile hypertension.

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## SPECIAL ARTICLE

# INDIA MODERNIZES HER MEDICAL EDUCATION

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BOSTON

INDIA is planning a promising experiment in medical education. An important accomplishment of the present government is the way in which the leaders are using constructively the enthusiastic nationalism that had so long been focussed on getting independence and could easily have dissipated into frustration after freedom was won. By channeling this backlog of energy into a positive program of development the country is making rapid progress and accepting changes that the people would normally have resisted. In the reaction against foreign ways of doing things the leaders are having to think through what is really best for India in medical education along with all other phases of life.

This was brought out clearly at the first meeting of a preparatory committee for the All India Conference on Medical Education held last November. The particular function of this committee was to prepare a new curriculum for Indian medical colleges, including a required year of internship. A distinguished group of medical educators from all over India gathered in Bombay. One of the first questions was, "How much should we be concerned with the recognition abroad of Indian degrees?" As the only non-Indian on the committee the question came to me. When I strongly advocated that the committee forget about foreign recognition of degrees for the time being and concentrate on developing the type of medical education that would be best for India there was immediate expression of relief around the table. I pointed out that foreign medical authorities would respect Indian medical education a good deal more if it was apparent that doctors were being trained to meet the needs of Indian villages rather than for specialized society practice on Harley Street in London or Park Avenue in New York. Once this basic point had been cleared away one could start thinking about medical education from a fresh and Indian point of view.

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### PLANNING FOR MEDICAL EDUCATION

For years there has been slow progress in planning for better medical education. A particular milestone was the report of the Bhore Committee on reorganizing medical care and health programs that was published during World War II. A major recent development occurred when the Rockefeller Foundation called a meeting of deans of medical colleges in the winter of 1954 in Bangalore. Out of this conference grew the recommendation that the Central Health Ministry organize the All India Conference on Medical Education in the fall of 1955. A preparatory series of meetings provided the necessary opportunities for planning and gathering data that made for intelligent thinking and decisions in the final meeting.

Throughout this period of planning certain fundamental ideas were accepted:

> A major revision in medical education is essential because the present system of education is patterned on what was being done in England fifty years or more ago. It is adapted neither to modern conditions nor to India.
>
> The production of doctors has to be greatly increased to provide medical care to residents of rural areas, who make up more than three fourths of India's population.
>
> Until better doctors are available most Indians will continue to rely on practitioners of the indigenous systems of medicine, the Vaidyas and Hakims, for their medical care.
>
> Certain fields of medical training need to be specifically emphasized even if it means reducing the time allotted to traditional subjects:
>
> > Preventive and social medicine should constitute a significant part of the training of each student and the practice of each doctor if the health conditions of India are to be improved with resources that can be mobilized.
> >
> > Pediatrics is a field that has received almost no attention but deserves an important place in the

curriculum, particularly because more than half India's population is less than fifteen years of age.

Psychiatry is a fundamental discipline that has been largely ignored. Many mental hospitals are run more as penal institutions than hospitals. General practitioners should be trained to handle mental-health problems as part of their practice.

The premedical training and selection of students will have to be changed to fit into present educational trends and at the same time to improve qualitatively the preparation of students. Decision has to be made about how long English should be the medium of instruction because there is progressively decreasing emphasis on English in basic education.

No effective change in teaching methods and program can be made unless there is simultaneous modification of the present system of examinations. There is entirely too much emphasis on examinations, and the methods used provide little more than an evaluation of the student's memory.

### Teaching Program in Preventive Medicine

In the spring of 1955 the Rockefeller Foundation organized a conference of teachers of preventive medicine in Delhi. The discussions led to basic agreement on the question of what an ideal teaching program in preventive medicine should be. At the request of the conference I prepared a sample syllabus, which was based largely on experience in developing a new curriculum at the Christian Medical College, Ludhiana. Some of the important features were as follows:

About once a month for students in the first two years there are monthly clinicosociologic conferences in which an interesting case is presented by a senior student. A representative of each department, starting with anatomy and physiology and running through the clinical specialties, discusses in ten minutes the contribution of his field to understanding of the patient's condition. A summary presentation by the department of preventive medicine traces the chains of causation that led to the existing condition and the possibilities of breaking the various links in these chains. The discussion concludes with the emphasis that responsibility to the patient does not cease when he is discharged from the hospital. Consideration is given to how prognosis can be influenced by appropriate control measures.

During the first half of the first year there is an introductory course of one hour a week in preventive medicine that is called human ecology. This deals with a general analysis of the relation of man to his environment, with appropriate emphasis on biologic, physical and social relations.

In the second half of the first year there is a course in biostatistics that includes three mornings in a village conducting a general health survey. The students use the data that they gathered themselves for their laboratory work in statistical calculations.

In the second year students start a long-term association with a single village family. They are taken to the village health center in groups of 25 for a two-hour laboratory session each week. Intimate friendships lead to a deep understanding of the economic, social and psychologic problems of family life in the village. To bring out these lessons the whole class meets for an hour of discussion each week. Two students present their families, and the class tries to find ways of helping on the basis of understanding of total needs.

In the third year the same program continues except that the emphasis is on sanitation. In addition to one hour a week of lectures in sanitation the class works out practical problems of village sanitation in the homes of the families.

In the fourth year, in co-ordination with the department of medicine, an integrated course on the epidemiology and control of communicable diseases is being developed.

In the fifth year the students are given a course in community health that includes discussions of maternal and child health, industrial health and school health.

The desirability of a co-ordinated outpatient service is recognized, and arrangements for students to follow outpatients in their homes are being made. This will be particularly important in medical schools in large cities, where it will be difficult to get medical students out to the villages.

Throughout the program attempts are made to integrate the preventive emphasis in the teaching of all departments. Nutrition is taught in co-operation with biochemistry. During their clinicopathological training students collect samples from their own families so that when they find something such as an ascaris ovum in a stool they will visualize more than an impersonal egg — to them it will be an ovum from a patient they know living in an environment they know.

All students are required to serve a year's internship after their medical course of four and a half years. This is to be a rotating service, with three months of the time spent in a rural health center operated under the department of preventive medicine.

### Rural Hospitals

An interesting experiment is being started at the Christian Medical College at Vellore in South India by Drs. Leroy Allen and Paul Brand. They are setting up a rural-style hospital integrated with preventive services in the surrounding villages. To prepare doctors for village service the emphasis will be on teaching the students simple ways of doing things and

how to use makeshift equipment in emergencies — for example, it has been found that an aluminum wash basin with a bulb appropriately placed makes an excellent operating-room light.

### Recommendations for Improved Medical Education

Obviously, to introduce this new teaching material it has been necessary to reduce teaching time in some subjects. In responses to a questionnaire sent out in preparation for the Conference on Medical Education it was found that teaching was very heavily weighted with anatomy and certain specialties that do not actually need to be learned until subsequent specialization.

When the All India Conference on Medical Education met in November, 1955, it passed a series of far-reaching recommendations that have been accepted by the Indian Medical Council and the Council of Provincial Health Ministers. In summary they deal with the following matters:

Improved methods of selecting students, giving emphasis to considerations other than grades in college examinations, are necessary.

Better premedical training is needed.

Curriculum hours are completely revised. Anatomy time is cut in half. Teaching methods should be radically changed, with less emphasis on lectures and more on seminars and practical work.

The need for changing the system of examinations is great, but the solution is not easy and must be approached experimentally.

There should be a full-time department of preventive and social medicine, with adequate facilities, including, wherever possible, urban and rural health centers and co-ordinated outpatient facilities. The syllabus discussed above was accepted as a model. A separate final examination is to be given.

Each medical college should have a separate full-time staff unit in each of the major clinical subjects. The members of these units are to receive adequate salaries so that they will not need to rely on private practice. The teacher-student ratio is to be increased to 1 teacher per 5 students as rapidly as teachers can be obtained.

Improved methods of selecting and promoting teachers were discussed, and it was agreed that their conditions of service should be improved.

Pediatrics should receive major emphasis, and separate departments and special wards should be provided.

The importance of post-mortem examinations in teaching was stressed. Among the measures recommended to increase the number of examinations was the possibility of special legislation.

Psychologic medicine and psychiatry are to be taught, and a special staff provided.

### Discussion

It may seem that the recommendations are so sweeping and ambitious that they will be impossible to achieve. An important consideration, however, is that most of the medical colleges of India are run by the Government. The few that are not are under the close supervision of official agencies. The recommendations of the conference have been accepted as official government policy. Therefore, the chances of getting action should be good.

The major difficulty will be in finding the personnel to carry out these ambitious schemes. There is already a great shortage of good teachers. The Government is constantly opening new schools; the total number has gone well over 40 in the past few years. Equipment and buildings can be provided, but good teachers will take time to train.

Perhaps the greatest contribution that the United States can make in helping India meet its health needs is through aid in producing teachers. Indians must be trained to teach the doctors, nurses and village health workers who are needed in increasing numbers to staff the ambitious development programs of the country. Fellowships are available, and appreciable numbers are coming to the United States for training. Much careful consideration has been and is being given to the quality of the training provided here. It cannot be emphasized too strongly, however, that medical faculties in America have a challenge for service that can have a lasting influence on the health of Asia. A personalized, sympathetic approach and a little additional effort to make the learning experience of Indians and others in this country more fruitful is a contribution that is in a unique way the privilege of the American medical profession today. There are also challenging short-term appointments available for specialists who would like to go to India to help organize departments in both preclinical and clinical subjects.

## MEDICAL PROGRESS

# PLASTIC SURGERY: TISSUE AND ORGAN HOMOTRANSPLANTATION

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BOSTON

THE important observation of Medawar[1] that a second homograft of skin from the same donor rabbit to the same recipient rabbit was rejected more rapidly than the first stimulated hope that perhaps a recognized biologic reaction could explain the mysterious "individual tissue specificity" originally theorized by Loeb.[2] This evidence of a specific sensitization of the recipient by the donor tissue and the antigen-antibody-like reaction in the rejection of the transplant has been the impetus for a series of further investigative projects on both sides of the Atlantic.

Among the earliest technics of study was parabiosis (1860),[3] the physical union between two animals of the same species. Permanent survival of animals in parabiosis was not achieved because one animal assumes dominance and acts as the recipient while the other, or donor, animal succumbs. The experimental embryologists, at the turn of the century, did produce successful parabionts in cold-blooded animals when fusion was performed during early embryonic life.[4] In studies concerned with growth, primitive limb buds, segments of spinal cord, optic cups and other tissues were transplanted between amblystoma larvae. The transplanted tissues survived and developed in the new host, established nerve and vascular connections, and functioned as normal tissues. In none of these investigations, however, were mammalian or adult tissues used.

Although many experimental and clinical homotransplants of skin and other tissues were undertaken in warm-blooded animals and man during the first four decades of this century, no reports of permanent survival were observed except between identical twins. One well documented report of successful skin grafts between identical twins was presented by Brown[5] (1937). Corroborative reports by other authors have appeared in the literature since that time, including one in which successful exchange of skin grafts was accepted as a legal proof of identity.[6] The life-saving use of a kidney homotransplant between identical twins has recently been carried out with dramatic success by the group at the Peter Bent Brigham Hospital.[7] Cartilage, cornea, fascia and bone were transplanted successfully, but these mesodermal tissues elicit a different reaction in the host. The mass of evidence that was reported during these years merely strengthened the concept that individuality begins in the fertilized ovum and remains specific in every cell of the adult animal.

For purposes of avoiding the confusion concerning the characteristics of various transplants, the terms *homostatic* and *homovital* were coined by Longmire.[8] The former refers to structural transplants of bone, cartilage, blood vessels, fascia and cornea whose purpose is to supply a framework that eventually may be replaced by host tissues. The latter refers to skin, kidney, lung and endocrine tissues whose usefulness depends on permanent survival of the cells of the transplant. It is in the latter group that the host-rejection response is elicited.

Skin and kidney, both in man and in animals, have been the most commonly used tissues in these studies. Skin has the advantage of transplantability by simple technic, can be observed directly throughout its course of survival and rejection, and is available for serial biopsies throughout its life span. However, it may not be the ideal tissue to use since its high antigenicity and its involvement in a variety of immune reactions complicates the interpretation of results. The kidney is useful for the study of organ homotransplantation because it is readily revascularized and its function can be measured accurately. Thyroid, parathyroid and adrenal tissues are also being investigated both as implants and as vascularized transplants,[9,10] but the results of studies of endocrine homotransplants have not been conclusive because most investigators have used implants instead of vascularized transplants.

Homovital tissues or organs may be transplanted either as nonvascularized implants or as transplants to which there is established immediate vascular continuity with the recipient. Skin homografts are transferred as implants to prepared raw surfaces. Kidney, thyroid gland and so forth may be vascularized by direct vascular anastomosis or may be implanted in the soft tissues of the new host.

Recent investigations on homotransplantation may be divided into the following categories:

Description and analysis of the recipient's local reaction to the foreign tissue and definition of the exact end point of survival of the homograft.

Determination of the nature of the antigen-antibody reaction and identification of the antigen or the antibodies responsible for the reaction between host and transplant.

Clinical and experimental efforts to prolong survival by reducing the antigenicity of the homograft or the antibody reaction in the host.

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### The Local Reaction

Loeb[11] was the first to describe the microscopical picture of the host reaction to the homotransplant. It is an acute, local, nonsuppurative, inflammatory reaction characterized by edema, heavy leukocytic infiltration, predominantly lymphocytic, and finally progressive dissolution of the graft. Loeb was aware that the picture of the local response in the host resembled an antigen-antibody reaction, but failed to observe the accelerated rejection of the second graft because he overlooked the need for using the same donor each time. He was seeking a sensitization of the recipient but considered the reaction unilateral in the recipient and nonspecific to the donor.

The primary skin homograft in the rabbit, as described by Medawar,[12] "invariably displays a major outburst of epidermal cell proliferation." The skin homograft to an animal that has already reacted to a homograft of skin from the same donor "undergoes complete suppression of cell division. The grafts survive in a 'vegetative' condition alone."

Direct microscopical visualization and photographs of the changes in acceptance and later rejection of the skin homograft have been possible by the transparent-chamber technic. The loose tissue on the back of the mouse to which the homograft has been transplanted is elevated and held between transparent discs. By transillumination, details of the new blood vessels, the graft and the cell migration can be followed.

Vascularization of the homograft in the transparent chamber is observed by the second or third day. By the ninth or tenth day thromboses appear, and the graft is rejected and destroyed. An increase in lymphocytes and plasma cells around the vessel accompanies the formation of the thromboses. Because of the association of lymphocytes and plasma cells with immune reactions, Conway et al.[13] have postulated that these cells are the carriers of immune bodies or toxins that initiate the thrombosis. Dicumarol given parenterally prevents the formation of thromboses but does not alter the rejection reaction. Cortisone decreases the cellular reaction but not the final occurrence of the rejection. Cortisone, anticoagulants and antihistaminic drugs thus modify the picture in homograft rejection and are reported to prolong survival of the graft for a day or so, but there is no evidence that the grafts are ever accepted permanently.

Direct observation of blood vessels in the homograft by the dissecting microscope has been reported in mice by Taylor and Lehrfeld[14] and in man by Converse and Rapaport.[15] A consistent end point of homograft survival has been stasis of blood flowing through the graft vessels at eight or nine days. This observation has been confirmed by Edgerton et al.,[16] using a refinement of the transparent-chamber technic. These workers consider the thrombosis reported by Conway and his associates to be a secondary manifestation of rejection and note that as perivascular cellular infiltration occurs, blood stasis and rejection of the graft follow rapidly.

Hume and Egdahl[17] studied the vascularized homotransplant of kidney in the dog. By sewing a zipper in the wound they were able to take daily biopsies of the graft. Premonitory microscopical changes in the transplants were observed even while function was still maintained. These changes are described as swelling and differentiation of endothelial cells in cortical vessels leading to ischemic tubular degeneration and finally tubular necrosis without glomerular changes. But, just as with the skin, perivascular cellular infiltration (lymphocytes) proved to be the indication of the imminent rejection reaction that initiates the decrease in function and its cessation, usually in twenty-four to seventy-two hours.

Dempster[18] has made a nice differentiation in the dog between the reaction to a homoimplant (nonvascularized) and homotransplants (vascularized) of kidneys, adrenal glands and ovaries.[19] The implant excites a classic foreign-body reaction leading to destruction and fibrosis, whereas the transplant of the same tissue calls forth the characteristic picture of rejection. The pattern of rejection (immune response) is the same for all three organs. Dempster has also observed that the survival time of an endocrine homograft is not influenced by an established endocrine deficiency in the recipient, as suggested by Halsted.[20]

### Nature of the Antigen-Antibody Reaction

This "second-set" phenomenon, the term used for Medawar's observation that the second skin graft from the same donor to the same recipient is rejected more rapidly than the first, has been confirmed by many other workers. The immune mechanism has proved very specific between animals even of the same species. But the still unidentified antigen is shared by many tissues of the body, any one of which will sensitize the recipient to another tissue from the same donor. Thus, the reaction is specific for the individual and not for the tissue.

Medawar[21] has found that intradermal injection of foreign homologous leukocytes confers a typical immunity toward later skin grafts from the leukocyte donor. The immunizing effect is eighteen times more effective when the leukocytes are given intradermally than when they are given intravenously. Intradermal or intravenous administration of red cells or nonviable white cells produces no measurable immunity. Billingham et al.[22] have demonstrated that homologous viable lymph-node tissue likewise confers specific immunity. The obvious conclusion is that immunity is conferred only by living cells. Gorer[23] has reported in man the development of antibodies to the donors' erythrocytes after the rejection of a skin homograft. Both donor and recipient (father and daughter) were blood Group A, Rh negative, and without demonstrable antibodies before the grafting

procedure. Thus, skin and erythrocytes probably share antigens even though the erythrocyte does not elicit the antibody response.

Dempster[24] and Simonsen[25] have shown that a previous skin graft will make a later kidney transplant behave as a second-set homograft, and, likewise, the kidney will sensitize the donor to skin from the same donor. Hardin[26] has demonstrated by the same method that skin and lung also share the antigen. Egdahl and Hume[27] have found that crosscirculation in dogs for as short an interval as five minutes will cause accelerated rejection of a later kidney transplant. They also report that crosscirculation established at the time of kidney transplantation in a sensitized pair of animals is associated with continued urinary excretion instead of rapid rejection. This stabilization of the transplant is thought to be due either to dilution or to destruction of the antibodies produced by the recipient that thus aborts or delays rejection reaction. The kidney shows no histologic changes until after separation from crosscirculation, when it undergoes rapid necrosis.

Lehrfeld et al.[28] have carried Medawar's original observation one step farther by transplanting the second skin homograft from the same donor but before the first has been rejected (mean survival time, eight and three-tenths days). Rejection of both homografts then occurs simultaneously, indicating the systemic nature of the reaction. The second homograft transplanted as rejection of the first is occurring fails completely; if transplanted after failure of the first, the rejection is accelerated as in the usual second-set reaction.

Skin homografts to areas devoid of lymphatics, such as the brain and the anterior chamber of the eye, will survive indefinitely. The observation suggests that the antigen must be carried through the lymphatics and probably lymph nodes before the rejection reaction is initiated. If, then, a skin homograft from the same donor is transplanted to an area of the host's body with normal lymphatic channels, a sensitization is established, and the primary graft will be destroyed. It is assumed that contact with the specific circulating antibody or sensitized lymphocytes initiates the rejection reaction.[29] The detection by Mitchison[30] of higher concentrations of sensitizing substance in the regional lymph nodes during homograft rejection than in nodes elsewhere emphasizes the relation of the lymph node to the rejection phenomenon.

Algire et al.,[31,32] in an interesting series of reports, have shown that, in mice, homografts of various tissues ("target cells") will survive indefinitely in a diffusion chamber if the porous walls exclude host cells from the graft. The "target cells" do not produce an immune reaction in the host but, on the other hand, will survive in an immunized host as long as host cells are excluded. "Target cells" exposed to "nonimmunized" host cells remain in good condition. The important host cells are lymphocytes, and the destruction of the "target cells" is by the immunized lymphocytes rather than the circulating noncellular antibodies.

These observations have been confirmed by Kiehn and Gutentag,[33] who, after enclosing homografts of bone in the buried chamber, observed uptake of radiophosphorus ($P^{32}$), an evidence of viability not found in the unprotected homograft.

When a series of skin grafts from the same human donor to the same recipient is done at intervals of two to five weeks, an intense erythematous reaction or flare appears in the area of the immediately preceding graft. This so-called "recall phenomenon," observed in many by Converse and Rapaport,[34] is a highly specific remembrance of previous sensitization and is similar in many respects to the delayed tuberculin reaction when an animal is reinfected with the tubercle bacillus. It is assumed to be a residual local accumulation of antibody that is slow to dissipate. That dissipation does occur is indicated by the disappearance of the recall phenomenon after three or four months.

Although current evidence suggests that absorption of the antigen through the regional lymphatics to the cells of the regional lymph nodes is an essential part in the rejection reaction to the homograft, Hume and Egdahl[17] demonstrated that the lymphatics are not essential for renal homotransplant rejection in the dog. Isolation of the renal homograft in a watertight plastic bag with only arterial and venous connections has failed to prevent destruction of the graft. The possibility that lymphatic connections have developed is recognized and is being investigated further.

Mitchison[30] has removed regional lymph nodes and found no change in host reaction to the homograft of skin but suggests that other tissues, spleen or other more remote nodes are responsible.

In an effort to isolate the circulating antibody Egdahl and Hume[27] have exsanguinated a dog at the height of the rejection reaction and injected the plasma directly into the renal artery of the donor's remaining kidney. No histologic or functional change was observed. The injection of recipient serum into the donor's vein had been done by Dempster[18] without change. Egdahl's purpose of direct injection in the renal artery was to avoid destruction or filtering of the antibody by other organs. It seems reasonable to assume that the total circulating antibody present at any one time in an immunized animal is insufficient to produce the rejection reaction.

The recent report of Bollag[35] claims the successful detection of circulating antibodies after skin homografting in rabbits. The method is a turbidity test highly sensitive to specific tissue antibodies circulating in the serum. The evidence of Medawar and Billingham strongly suggests the existence of acquired antibodies, and Gorer[23] demonstrated red-cell and white-cell agglutinins in skin homografts in mice, but this is apparently the first in vitro demonstration of antibodies that has appeared in response to grafts of normal tissue.

### Prolongation of Survival of the Homotransplant

Once the end point of survival of the homograft and something of the nature of the antigen-antibody reaction between the host and the graft have been defined more accurately the obvious next step is to determine what changes in the host or the graft will prolong graft survival. Permanent survival of skin grafts and kidneys exchanged between human identical twins has been mentioned. Closely inbred laboratory animals exhibit the same tolerance to the exchange of tissues as occurs in identical twins. Algire et al.[31] have suggested that the more "foreign" the antigen and the greater the phylogenetic distance of the organisms, the more active that antigen will prove to be. The closer phylogenetically the antigen is to the host, the weaker the antigen and the reaction to it. Thus, the bacterial and protozoal antigens are the most active, and the homograft the least active of the antigens. The active antigens call forth abundant antibodies, which can be identified in the blood stream; the less active homologous antigens provoke so little antibody production that effective concentrations are present only in the immediate vicinity of the homogenous tissue and the lymphocytic cells reacting to produce the antibody.

Good and Varco[36] have reported prolonged survival of skin homografts to human recipients with agammaglobulinemia. This observation on patients incapable of producing antibodies either to bacteria or to foreign skin is further evidence that the intolerance of the recipient to the foreign skin is related to an immune reaction. Skin from the patient with agammaglobulinemia is normally antigenic and is rejected when transplanted to a normal host.

Finally, the natural phenomenon of dizygotic freemartin cattle[37] has an important bearing on the understanding of homotransplantation because both skin and kidney have been transplanted successfully between these twins that are of opposite sex and develop from separate ova. An intermingling of fetal circulation proved by the post-partum identification of circulating blood cells of dual origin establishes a permanent tolerance early in embryonic life that permits the later exchange of homografts. Although unexplained, the female of the pair is usually sterile.

Billingham et al.[38] have imitated nature's whimsey by inducing an "acquired tolerance" in divergent strains of mice by the intra-uterine injection of the fetus with homologous cells. Tolerance to skin homografts established by this method is donor specific and not due to a fundamental change in the recipient's immunologic response. That the antigenicity of the "tolerated" graft remains specific is proved by the spontaneous rejection of the homograft when tissue from a third animal sensitized to the original donor is injected into the host.

Whether "tolerance" between mother and child may occur because of intermingling of fetal and maternal circulation is still unknown but is a lead that will no doubt be followed.

The evidence that immunologic differentiation develops only as the embryo matures and may even be incomplete at birth has led to a study of skin transplantation in day-old chicks. Permanent survival of skin homotransplants has been achieved in a significant percentage of these chicks. The survival rate decreases sharply after the second day but has succeeded as late as the fourteenth day.[39]

The prolonged or permanent survival of homotransplants has not been reported in most other experimental situations.

Alteration of the physical state of the donor tissue by freezing, heating and so forth has failed to increase its survival. It is questionable whether the skin survives after these insults. A nonviable graft may be tolerated as a nonantigenic membrane until it is rejected. There is a recent report by Conway et al.[40] that the specificity of mouse-skin homografts preserved in tissue-culture mediums containing homologous embryo extract diminishes with increased periods of preservation. Prolongation of survival time of treated whole-thickness skin homografts as compared to the nontreated controls is reported.

Other efforts to diminish the antigenicity of the homograft and alter the reaction of the host include total-body irradiation of the donor and recipient, splenectomy, blocking of the reticuloendothelial system by trypan blue and thorium dioxide, suppression of leukocytes by nitrogen mustard and alteration of the immune response by ACTH and cortisone. Several investigators report increases in survival time, but no permanent survival of skin homografts.

Werder and Hardin[41] have applied consecutive skin homografts to the same animal from a donor mouse at different intervals. They report an increasing percentage of survival of the grafts after several consecutive graftings. It is postulated that an "immunoparalysis" is established by the repeated grafting, which holds the immune mechanism in abeyance. Similar increases in survival of skin homografts were observed when the donor animal was injected with homologous skin extracts prepared from 24 mice selected at random. The injection was given at intervals before and after the grafting procedure.[42]

Mitchison[30] has suggested that the successful homotransplantation of cancer in the laboratory animal may be due to an overproduction of antigen by the tumor cells that in turn produces an immunoparalysis and host tolerance of the transplant.

"Skin types" analogous to blood types have not been demonstrated either clinically or by chemical or tissue-culture methods. Longmire et al.[43] transplanted skin from 71 different donors to a single recipient but failed by this method to find any compatibility between the host and any of the grafts. Statistical analysis indicated that if groups do exist there are no less than 23.

Medawar,[44] in 1944, showed experimental evidence that the survival time of homografts varied inversely with the dosage. This observation is in keeping with the concept of an immune reaction in homograft rejection and has been confirmed by Lehrfeld et al.[28] The obvious practical conclusion to be drawn from this evidence is that small amounts of skin from multiple donors is preferable to large amounts from one donor since the total dosage of specific donor antigen will be reduced.

## Summary and Conclusions

Clinical and experimental evidence gathered in the past decade and a half indicates that the rejection of homotransplants is on the basis of an immune or antigen-antibody reaction. This reaction is host and donor specific but not specific for any one tissue. The antigen is common to the living cells of many tissues of the same individual.

In the human being, permanent survival of skin and kidney homotransplants has been reported between identical twins and in patients with agammaglobulinemia whose immune response is deficient. Successful transplants of structural tissues (cornea, cartilage, fascia, bone and so forth) are possible because the survival of the cells of the transplant is not necessary for functional usefulness of the graft and because eventually the graft may be replaced by host tissues.

The end point of survival of a homograft is marked by local leukocytic infiltration, predominantly lymphocytic, slowing of the blood flow locally and, finally, dissolution of the homograft. The lymphocyte plays an important part in the development of the host sensitivity and rejection of the homotransplant. Serum antibodies are ineffective in destroying the homograft; only sensitized cells of the host can cause homograft rejection.

Permanent survival of homografts is reported between laboratory animals of closely inbred strains and between pairs of dizygotic freemartin cattle that share a fetal circulation and develop a tolerance to each other's tissues. This "acquired tolerance" has been duplicated experimentally by intra-uterine injection of the fetus with homologous cells.

Other efforts to prolong the survival of homografts have been directed at altering or suppressing the host antibody response and at reducing the antigenicity of the transplant. Increases in survival time of the homografts have been reported, but permanent successes have been inconsistent.

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# MEDICAL INTELLIGENCE

## AMMONIA INTOXICATION IN A PATIENT WITH CONGESTIVE HEART FAILURE RECEIVING AMMONIUM CHLORIDE ORALLY*

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THE liver in chronic congestive heart failure is usually enlarged and often tender, and shows histologic alterations of the lobules, particularly in their central portion.[1-3] In more advanced cases the morphologic changes spread peripherally and may include fibrosis of the periportal areas as well. The

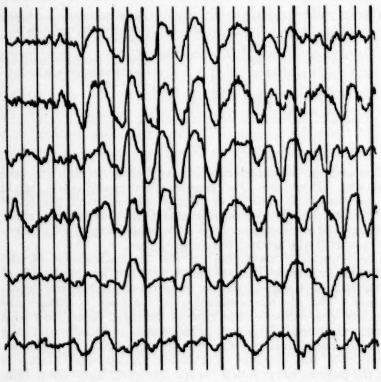

FIGURE 1. *Electroencephalogram in Impending Hepatic Coma, Showing an Abnormal Slow Record.*

physiologic counterpart of the anatomic lesion has been well documented by numerous investigations.[1,4-7] More recent studies have shown that the degree of altered function and morphology tends to correlate with the severity of the heart failure.[1,5]

Evidence of cerebral dysfunction such as drowsiness, confusion, lethargy and even coma is occasionally associated with severe congestive heart failure. A reduction of total cerebral blood flow and an increase in cerebrovascular resistance has been reported in such cases.[8] The possible role of ammonia in the etiology of the reduced cerebral metabolic rate and cerebral dysfunction observed in hepatic coma has received considerable attention.[9-12] Bessman and Evans[13] have demonstrated an increase of arterial ammonia levels in patients with congestive heart failure, and have suggested that the cerebral dysfunction may be due to the associated hepatic insufficiency in some cases.

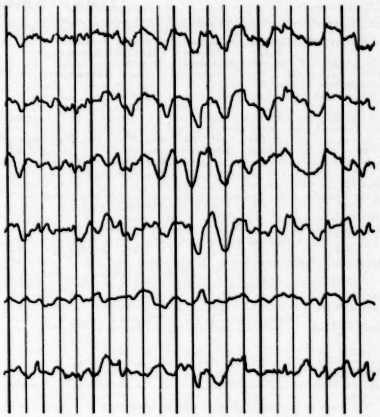

FIGURE 2. *Electroencephalogram in Deep Hepatic Coma, Showing a Grossly Abnormal Record.*

This report presents the findings in a patient with cardiac decompensation of at least four years' duration who was given ammonium chloride by mouth and in whom classic signs of hepatic insufficiency culminating in coma and death subsequently developed.

### CASE REPORT

N.E., a 50-year-old man, was admitted to the District of Columbia General Hospital on September 21, 1955, complaining of severe shortness of breath of 6 weeks' duration. Since the age of 17 he had had hypertension with dyspnea, which limited strenuous physical activity. Except for the dyspnea he was relatively asymptomatic until 1951, when vertigo developed and he complained of headaches. The dyspnea increased, and he noted dependent edema and orthopnea and experienced attacks of paroxysmal nocturnal dyspnea. He became progressively worse and was placed on a low-salt diet and given digitalis and, in addition, received diuretics, sedatives and hypotensive agents. Except for nocturia there was no history of impaired renal function. The dietary intake had been good, and indulgence in alcoholic beverages was denied.

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Physical examination revealed a well nourished man who was alert and co-operative but moderately dyspneic. Funduscopic examination disclosed marked arteriolar spasm, with recent and old hemorrhages and exudates. The heart was enlarged, the apical impulse extending to the anterior axillary line; the pulmonic 2d sound was accentuated, and there was a gallop rhythm. Moist, crackling rales were heard at both bases. The liver was tender and palpable, the edge extending 5 or 6 cm. below the right costal margin, and there was shifting dullness and a fluid wave. There was + + pitting edema of the lower extremities.

The temperature was 99.2°F., the pulse 120, and the respirations 18. The blood pressure was 280/180.

Examination of the blood disclosed a white-cell count of 4950, a hemoglobin of 16.5 gm. per 100 ml. and a hematocrit of 55 per cent. The blood serologic test for syphilis was negative. The sedimentation rate was 9 mm. per hour, blood urea nitrogen was not significantly changed. On the following day he became more stuporous, and the characteristic odor of fetor hepaticus was noted. A repeat lumbar puncture again showed only an increased cerebrospinal-fluid pressure (equivalent to 320 mm. of water).

The ammonium chloride was discontinued, the patient having received a total dose of 20 gm. in 3 days. Laboratory studies on the 5th hospital day included blood pH, ammonia and glutamic oxalacetic transaminase. Cerebral blood flow and oxygen utilization were determined, and an electroencephalogram (Fig. 1) and a liver biopsy were obtained. Two days later, because of the development of coma, 20 gm. of monosodium glutamate was given intravenously. The procedures mentioned above were repeated before and after the glutamate was administered. A summary of the laboratory findings is presented in Table 1, and the repeat electroencephalogram in Figure 2.

TABLE 1. *Summary of Laboratory Findings.*

| DATE | CEREBRAL BLOOD FLOW | CEREBRAL OXYGEN CONSUMPTION | CEREBRAL VASCULAR RESISTANCE | MEAN ARTERIAL BLOOD PRESSURE | AMMONIA | | pH | | SERUM GLUTAMIC OXALACETIC TRANSAMINASE | COMMENT |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ARTERIAL | VENOUS | ARTERIAL | VENOUS | | |
| | *ml./100 gm./min.* | *ml./100 gm./min.* | *mm. Hg. /ml. of blood/100 gm./min.* | *mm. Hg.* | *microgm. /ml.* | *microgm. /ml.* | | | *units/ml.* | |
| 9-25 | | | | | | 1.5 | | | 40 | Onset of lethargy & tremor; patient had received 20 gm. of ammonium chloride. |
| 9-26 | 37.3 | 2.3 | 5.0 | 185 | 2.0 | 1.5 | 7.37 | 7.33 | | Stupor, lethargy & flapping tremor more pronounced |
| 9-28 | 42.5 | 2.3 | 4.2 | 177 | 1.0 | 0.8 | 7.47 | 7.45 | | Patient comatose — before administration of sodium glutamate |
| 9-28 | 50.6 | 2.4 | 3.6 | 180 | | 0.2 | 7.46 | 7.44 | | Patient comatose — after administration of sodium glutamate |
| Normal value* | 54.0 | 3.5 | 2.1 | 86 | <1.0 | <1.0 | 7.40 | 7.35 | 5-33 | |

*Obtained in normal patients of similar age group.

and the blood urea nitrogen 20 mg. per 100 ml. The urine gave a + + + + test for albumin and had a specific gravity of 1.026; the sediment contained 4 granular casts and 2 white cells per high-power field. The carbon dioxide combining power was 63 vol. per cent; the sodium was 136 milliequiv., the potassium 5 milliequiv., and the chloride 109 milliequiv. per liter, and the fasting blood sugar was 112 mg. per 100 ml. Liver-function tests disclosed 42 per cent retention of bromsulfalein and an alkaline phosphatase of 5.6 units. The total protein of the blood was 6.3 gm. per 100 ml., with an albumin of 3.8 gm. and a globulin of 2.5 gm. The serum bilirubin, prothrombin time and total cholesterol were within normal limits. X-ray examination showed the heart to be markedly enlarged, with evidence of bilateral pulmonary congestion. An electrocardiogram disclosed hypertrophy of the left ventricle and an occasional premature ventricular contraction.

On admission the patient was placed on a low-salt diet, continued on maintenance digitalis and given a mercurial diuretic. In addition both reserpine and Ansolysen were prescribed. On the following day ammonium chloride, 2 gm. orally 3 times daily, was started. He responded well to therapy, and the dyspnea and orthopnea decreased. There was regression of the edema, and the blood pressure fell to 150/100 on the 3d hospital day.

On the 4th hospital day behavioral changes were noted. The patient became stuporous, confused and occasionally hyperactive. A gross resting tremor of the upper extremities appeared, and flapping movements of the hands were noted when the arms were extended. Except for hyperactive reflexes, the neurologic examination was noncontributory. Lumbar puncture disclosed only an elevated cerebrospinal-fluid pressure (equivalent to 360 mm. of water). A repeat

The patient remained in coma and died on the 7th hospital day. Permission for post-mortem examination could not be obtained. The liver biopsy showed well preserved hepatic architecture, with minimal fatty infiltration, small focal areas of necrosis and only a slight amount of bile retention, particularly around the central vein.

The laboratory data, before the discontinuance of the ammonium chloride, demonstrated an elevation of the blood ammonia and a slight increase in glutamic oxalacetic transaminase. The electroencephalogram disclosed a diffuse abnormally slow activity; the rate of cerebral blood flow and oxygen consumption were significantly reduced, and the cerebrovascular resistance markedly elevated. On discontinuance of the ammonium chloride the arterial ammonia fell; the patient nevertheless lapsed into profound coma. The administration of sodium glutamate was associated with a further reduction of blood ammonia level, but without significant change in the clinical status, the rate of cerebral oxygen utilization or the electroencephalogram.

## DISCUSSION

The coma in the present case may have been due to an intracerebral hemorrhage, hypertensive encephalopathy or hepatic insufficiency. Intracerebral hemorrhage seems unlikely since there were no localizing signs before the development of coma. The markedly elevated mean arterial pressure and the high cerebrovascular resistance favor hypertensive encephalopathy. However, the development of cerebral

dysfunction, fetor hepaticus and flapping tremor on ammonium chloride therapy and the changes in the electroencephalogram strongly support hepatic insufficiency as the causative factor.

Phillips and his associates[12] have demonstrated that the administration of ammonium chloride to patients with cirrhosis may induce neurologic changes similar to those observed in patients with advanced hepatic insufficiency. In such patients, however, the mental state usually returns toward normal when ammonium chloride is discontinued; it is interesting that despite the fall in blood ammonia in the present case coma persisted. It is generally agreed, however, that the level of blood ammonia does not accurately parallel the patient's neurologic status. The administration of sodium glutamate, even though it was associated with a further decrease in blood ammonia, did not influence the clinical state or the electroencephalogram, or increase the cerebral oxygen utilization. We have noted a similar lack of response to sodium glutamate in other patients with hepatic coma.[14]

The reduced cerebral oxygen utilization cannot be ascribed to inadequate delivery of oxygen, since determinations before and after the administration of glutamate revealed an increase in the cerebral blood flow without a concomitant rise in oxygen utilization. In addition, studies of cerebral hemodynamics during induced hypotension have shown that the cerebral metabolic rate may be unchanged, despite a significant reduction in the rate of cerebral blood flow below that observed in this patient.[15] It is possible that the reduction in total cerebral oxygen consumption was due to the congestive heart failure and the presence of cerebrovascular disease.[16] However, Moyer, Miller and Snyder[17] did not confirm reduced cerebral blood flow or cerebral oxygen utilization in 20 patients with hypertension associated with heart failure. Novack and his associates[18] also failed to detect significant differences in cerebral hemodynamics or metabolism in 15 patients in congestive heart failure when the results were compared with those obtained in a control group. Therefore, it seems reasonable to infer that the reduction of cerebral metabolism in our patient was most probably due to hepatic insufficiency secondary to congestive heart failure and the administration of ammonium chloride.

In any event it seems advisable, from this and previous experience, to use ammonium chloride cautiously in patients with cardiac failure presenting cerebral manifestations or severe impairment of liver function.

### Summary

A patient with chronic congestive heart failure due to hypertensive cardiovascular disease, with no evidence of primary hepatic disease, is described. Ammonium chloride administered by mouth was followed by the development of the classic picture of hepatic insufficiency culminating in hepatic coma and death. Studies are presented of the cerebral hemodynamics and metabolism, blood ammonia levels and electroencephalogram before and after the administration of sodium glutamate. The role of ammonia as a possible factor in the etiology of the cerebral manifestations of cardiac failure and hepatic insufficiency is discussed.

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## CHOLERIFORMIC MONSTER

Henry J. L. Marriott, M.D.*

BALTIMORE

WHEN one adds a verbal offspring to an already overpopulated vernacular, one should be very sure what one is doing. As Fowler says, "word-making, like other manufactures, should be done by those who know how to do it; others should neither attempt it for themselves, nor assist the deplorable activities of amateurs by giving currency to fresh coinages before there has been time to test them." One of the latest monsters to rear its ugly bulk is "choleriformic." This has already been born[1] and blessed,[2] and it is high time for it to be drowned. The word is intended to mean choleralike, which is farther than even the tired elastic of verbal genetics can stretch.

There appear to be four good reasons why this "word" should never have sprung to life. To begin with there are already three terms meaning choleralike

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to be found not only in Stedman, Dorland and Gould but also in Webster: choleraic, choleroid and choleriform. There is certainly no semantic gap asking to be filled.

The other three reasons are to be found in the creature's anatomy. To begin dissection at its tail, formic means pertaining to ants (*formica,* an ant). Compound words making use of the stem of *forma,* shape, to convey the idea of resemblance, end in -form, as ensiform and falciform. Choleriformic can only mean, if any meaning can be wrung from it, a dysentery affecting or caused by ants. Indeed, in future discussions on the etiology of ants-in-one's-pants, one supposes it will now be necessary to consider the choleriformic syndrome.

Next, the monster is hybrid, for *cholera* is Greek whereas *forma* (or *formica*) is Latin. Not that all hybrids are avoidable or even undesirable, but best coinage still requires the wedding of words of the same language. The Greek equivalent of -form is -oid and is common to many medical terms: xiphoid, sigmoid, carcinoid and so forth. Choleroid is therefore demonstrably a better coin. Any number of etymologic bastards already adorn the medical vocabulary, such as idioventricular, granulocyte and commissurotomy, but this is no reason to add unnecessarily to the illegitimate breed.

Finally, if cholera is to be compounded with forma, there is no justification for -i- as the connecting link, for it belongs to the stem of neither of the compounding words; if one must have this mixed marriage, choleraform is to be preferred. There are any number of creaking joints in established medical terms, such as sino-atrial for sinu-atrial, but this is no excuse for more pieces of bad workmanship.

When all is said and done it is hard to beat the simple, anglicized, unmistakable "choleralike."

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## BRIEF RECORDING

## Brain Tumor in the Newborn Infant*

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CEREBRAL hemorrhage in the newborn infant is never without cause, but attempts to demonstrate such a cause are often fruitless. In the following case an unusual cause was demonstrated.

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### Case Report

J. G., a 22-year-old gravida 1, para 1, with expected date of confinement on June 1, 1955, was admitted to the hospital on May 4, stating that in an automobile accident that day she had been thrown against the dashboard. Labor started approximately 10 hours after the accident and was followed by slight vaginal bleeding. The prenatal course was complicated by a threatened abortion, for which she was hospitalized elsewhere.

The blood pressure was 130/80; there was a vertex presentation, with a fetal heart rate of 144 per minute. A definite placental bruit was heard. The abdomen showed uterine enlargement slightly under term. Pelvic examination revealed a 6-cm. dilatation, station plus one, with the head engaged. The membranes were ruptured during examination; the amniotic fluid was blood tinged.

Labor lasted for about 6 hours. There was 1 loop of umbilical cord around the baby's neck. Delivery was accomplished from the left occiput anterior position, by low forceps, under saddle-block anesthesia. There was a marginal placenta praevia.

The baby, a male weighing 2.9 kg. (6 pounds, 10 ounces), was somewhat hyperactive but without other abnormality. Routine newborn care was given. Forty hours after delivery respiratory distress and cyanosis were noted. The anterior fontanel was bulging, and all suture lines separated. A subdural puncture revealed frank blood bilaterally, and blood continued to drip from the needle marks, with some improvement. The baby was placed in an incubator; vitamin K was administered, but its condition became worse and it died 50 hours after birth.

Autopsy 10 hours later revealed a well nourished, well developed infant, significant findings being limited to the brain. There was a minimal occipital cephalohematoma. The entire surface of the cerebral hemispheres was covered by subarachnoid hemorrhage, and the left lateral ventricle was distended with blood. The entire left temporal lobe and the middle portion of the parietal lobe were soft, necrotic and friable. There was marked cerebral edema. The dural sinuses, the tentorium and the falx were intact, and there was no evidence of injury to any blood vessels. There was no subdural hemorrhage.

Microscopical sections from the diseased area revealed a

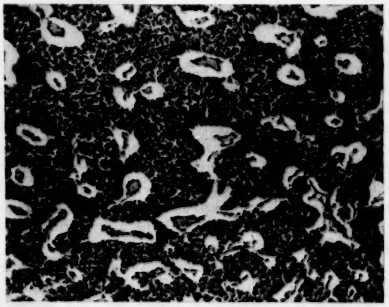

Figure 1. *Photomicrograph (X70), Showing Tumor Composed of Scattered Spindle-Shaped Cells, Palisaded in Areas around Large, Thin-Walled Blood Sinuses (Reproduced through the Courtesy of the Armed Forces Institute of Pathology, Washington, D.C. — Negative* 55-23585).

tumor composed of spindle-shaped cells scattered at random and in areas palisaded around large, thin-walled blood sinuses (Fig. 1). This lesion was finally identified as an ependymoblastoma.

### Discussion

Congenital tumors are rare, especially congenital

brain tumors. Tumors of ependymal origin seen in young children are most commonly papillomas of the choroid plexus or cysts lined with ependyma, and could more justly be classified as developmental defects instead of tumors.[1-6] Occasional medulloblastomas and "malignant gliomas"[7,8] are found, even in infants as young as three weeks. Ependymomas and ependymoblastomas are also occasionally reported.[4,9-11] Maisel and Lamm[9] report the case of a child eleven months old with a tumor of the cerebellum very similar to that described above. However, no report was found of a newborn child with a tumor of the brain of any kind.

In view of the vascularity of the tumor, it is considered that it was the cause of the bleeding. The accident, which could have started the bleeding from this lesion, adds to the difficulty. It is doubtful, however, if the trauma was severe enough, in view of the absence of injury to the mother. There was no evidence of obstetric trauma to account for so much bleeding. The partial placenta praevia appears to have been incidental.


### Summary

A case of intracerebral hemorrhage in a newborn infant secondary to a brain tumor is presented.


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## CURRENT CONCEPTS IN THERAPY*

### Sedative-Hypnotic Drugs. III. Paraldehyde and Methylparafynol

PARALDEHYDE, introduced into medicine by Cervello[1] in 1882, rapidly became and has remained one of the most useful hypnotics in medical practice. Its quick, smooth action and relative safety frequently make it the hypnotic of choice in acute excitement and in situations where a quick hypnotic effect is desirable. It is commonly the favorite of the intern because of its wide dose range, quick, apparently physiologic action, freedom from serious toxic effects and uniform efficacy. It is useful for controlling insomnia, excitement, agitation, delirium, convulsions and even severe pain, in which its powerful hypnotic effect leads to relaxation and sleep. It is most useful for insomnia of Types 1 and 3.†

Paraldehyde, a polymer of acetaldehyde, is a colorless, transparent, inflammable liquid that decomposes to acetaldehyde when exposed to light and air. Unfortunately, it has a burning, disagreeable taste and a pungent, though not unpleasant, odor and is irritating to mucous membranes. Its oral use in the presence of esophagitis, gastritis, gastric or duodenal ulceration or nausea and vomiting creates more irritation and is usually not advisable.

After ingestion paraldehyde is rapidly absorbed, and its effect is prompt. Usually, in ten to fifteen minutes the patient is asleep; therefore, patients should be in bed when the drug is administered. After absorption, most of the drug is destroyed in the liver by being converted into acetaldehyde, which in turn is metabolized to carbon dioxide and water. Smaller amounts are excreted by the lungs and kidneys. In the presence of liver damage destruction is slowed, and larger amounts are excreted by the lungs.[2] There is recent evidence that the liver in the presence of disulfiram (Antabuse) is unable to destroy paraldehyde as effectively, thus prolonging its action and increasing the pulmonary excretion.[3] In the presence of liver disease the drug has a more profound effect and can be toxic even in the customary dose. It is wise to avoid its use in the presence of liver damage.

Although pulmonary excretion of the drug is secondary it can, in the presence of a decreased ability of the liver to metabolize it, assume a very important role. If there is serious pulmonary disease with ventilatory insufficiency the added burden of paraldehyde excretion, which in itself may prove somewhat irritating to mucous membranes, can constitute a real hazard. It is not wise, therefore, to give large doses of paraldehyde to patients in severe asthmatic attacks.

Renal excretion is very minor and even in the presence of liver damage does not assume a much more important role. Paraldehyde may be safely given to patients even in the presence of severe renal damage.

The taste, mucous-membrane irritation and disagreeable odor exhaled by patients receiving paraldehyde prevent its widespread use and have made it a seldom abused drug. Although it is one of the safer hypnotics, death has occurred from doses as small as 12 ml. in a patient with liver disease; 30 and even 100 ml., however, have not been fatal to other patients.

*Prepared under the supervision of the *Journal's* Committee on Advertising.

†The four patterns of insomnia were defined in the first discussion of the sedative-hypnotic drugs, in the September 13 issue.

Whenever possible paraldehyde should be given by mouth. The disagreeable taste is relieved somewhat by mixture with shaved ice, and iced or cold drinks of juice, tea, milk or wine. The oral dose is 8 ml. but may vary from 3 to 20 ml., depending on the patient and the condition being treated. Larger doses are required in convulsions, delirium and excitement and in the presence of severe pain. It can be given by rectum as a suppository (Paraloids) containing 5 ml., in an olive-oil or mineral-oil retention enema or dissolved in physiologic saline solution. Unless the mucous membrane, especially near the anus, is anesthetized the irritation from the paraldehyde can lead to expulsion. Frequently, the addition of 1.0 ml. of benzyl alcohol to the enema supplies sufficient temporary local anesthesia to prevent expulsion. If this does not prove satisfactory a more effective, longer-acting local anesthetic may be employed. The rectal dose is 10 to 20 ml.

Occasionally, it is necessary to give paraldehyde intramuscularly. The drug is highly effective by this route but very irritating to tissue. It is essential that injections avoid the vicinity of nerves if severe nerve damage is to be avoided since paraldehyde behaves like alcohol in this respect. Individual injections larger than 3 ml. should be avoided; it is better to give two smaller injections. Larger amounts lead to tissue necrosis, abscess or extremely painful lesions, which are slow to heal. The intramuscular dose is 4 to 6 ml. of the sterile fresh solution.

Paraldehyde can be given intravenously. This mode of administration is much less desirable, and sudden death from right-sided heart failure has been reported. For intravenous use a dose of 1 to 4 ml. of the sterile fresh solution is dissolved in 0.9 per cent sodium chloride solution in a ratio of 1:10, and the dose slowly run in while the patient is carefully observed for any pulmonary or circulatory embarrassment.

Since paraldehyde readily decomposes to acetaldehyde it is essential, for parenteral administration, that fresh sterile drug be used if serious toxic effects, especially on the lungs from the highly toxic acetaldehyde, are to be avoided.

Methylparafynol (Dormison), one of the newer hypnotics, was introduced into therapy in 1951 by Margolin.[4] It is an unsaturated aliphatic carbinol dispensed in capsules as a clear, somewhat oily liquid. It has an unpleasant burning taste and is irritating to mucous membranes. Although methylparafynol has approximately twenty times the potency of paraldehyde and is 40 per cent as active as pentobarbital in human beings it is a weak, short-acting hypnotic whose depressant effect is readily antagonized by caffeine. Neurologists have found that it has a good, but not unique, anticonvulsant effect. It is useful in Type 1 insomnia.

On the basis of early laboratory and clinical studies methylparafynol was thought to be a very safe drug. More recent laboratory studies and wider experience in human patients, including 1 fatal case, reveal that the drug has much more inherent toxicity than was at first apparent. Liver cells in laboratory animals show alteration, and the cephalin flocculation test becomes positive in some patients receiving the drug.[5] Although animal studies show a low order of toxicity 5 gm. has produced a fatal case in a human subject, presumably by cardiac arrest, thus indicating that it can be six to ten times more toxic in human beings than was previously suspected.[6]

Methylparafynol is supplied as capsules containing 250 or 500 mg. In a dose of 250 mg. it has a sedative effect, but most patients require 0.5 gm., and an occasional patient 1.0 gm., for effective hypnotic action. Patients frequently complain of mild gastric irritation, burning, belching and unpleasant aftertaste. Another disturbing feature is irregularity of action, some patients getting an excellent and others a poor response on the same dose. Furthermore, this irregularity of action is often observed in the same patient.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

## CASE 42451

### PRESENTATION OF CASE

A thirty-seven-year-old gravida 9, para 4, was admitted to the hospital because of menorrhagia and dysmenorrhea.

Six months previously she was seen in the Outpatient Department because of menorrhagia and dysmenorrhea. Pelvic examination was negative. Three months previously she had had a spontaneous abortion two months after becoming pregnant. A subsequent dilatation and curettage was done at another hospital. After this procedure the uterus was packed. Two weeks later she had what she considered a normal menstrual period, with dysmenorrhea and a moderate flow that lasted for three days. Two months before entry there was severe, crampy pain in the lower abdomen that was associated with urinary frequency and lasted for four days. This was followed by a three-day menstrual period with excessive flow, including clots that required sheets and towels. One month before admission, because of an even heavier flow that was accompanied by abdominal cramps and lasted for a week, her physician gave her "hormone shots." Three or four days later there was a slight brownish discharge from the vagina that persisted until two weeks before entry, when she had a period lasting three days with a small amount of brownish discharge. Subsequently, there was no bleeding.

The patient's periods had always been regular every twenty-four to twenty-six days, lasting for five days and requiring three or four pads a day. The last normal pregnancy was three years previously. Eight years before admission a right salpingo-oöphorectomy and appendectomy were performed because of a simple ovarian cyst.

Physical examination showed a healed right paramedian abdominal incision. Pelvic examination revealed the uterine fundus to be more prominent on the right, where there was a firm, nontender egg-sized mass; the cervix was eroded; a slight cystocele was present.

The temperature was 98.6°F., the pulse 72, and the respirations 18. The blood pressure was 120 systolic, 78 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 11.4 gm. per 100 ml. and a white-cell count of 8900. Cytologic examination of a vaginal smear for malignant cells was negative.

An operation was performed on the second hospital day.

### DIFFERENTIAL DIAGNOSIS

DR. ARTHUR T. HERTIG*: On the basis of the history alone there are several possible explanations for the symptoms that brought the patient to the hospital. She may have had a single, large polyp of endometrial type, a pedunculated adenomyoma, with its mixture of smooth muscle and endometrium, or a pedunculated leiomyoma covered by endometrium. Such lesions can, on occasion, cause the combined symptoms of menorrhagia — prolonged bleeding at the time of normal menstruation — and dysmenorrhea. Menorrhagia is caused by several other pathologic lesions, one of which is so-called adenomyosis or "direct" endometriosis — the presence in the myometrium of nonfunctioning, noncyclical basal endometrium derived from the endometrium itself. Dysmenorrhea is a relatively uncommon clinical manifestation in a patient thirty-seven years of age. When it is acquired along with menorrhagia, the single most common cause is adenomyosis of the uterus. Both the age and the history suggest this diagnosis. I should like to ask if there is any information in the history about whether the dysmenorrhea was acquired at some time during adult life or whether the patient had always had it.

DR. ROBERT E. SCULLY: The dysmenorrhea appeared within two years before admission.

DR. HERTIG: This is in keeping with adenomyosis, although it is also possible that it was associated with true endometriosis — the presence of ectopic endometrium throughout the pelvic peritoneum, particularly in the ovary. On the basis of the first sentence in the protocol I doubt if the patient had true endometriosis, because she was not infertile.

Another cause of menorrhagia is failure of the corpus luteum to involute, resulting in a condition called chronic menstruation in which the endometrium fails to involute and fails to regenerate from the progestational stage. Inflammation of the endometrium, after either abortion or delivery, may also produce menorrhagia. We know that the patient had nine pregnancies with 4 full-term children, presumably living.

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Is it fair to ask if there are any data giving validity to the diagnosis of a complete or incomplete abortion? Was the patient really pregnant, and how much tissue was removed at the time of the dilatation and curettage performed at the other hospital? On these data depends the interpretation of the remainder of the history.

DR. SCULLY: The pathological report from the other hospital reads as follows: "The curettings consist of decidualike tissue with extensive necrosis and inflammatory change compatible with the end stage of a recent pregnancy."

DR. HERTIG: I judge that there was no morphologic evidence of trophoblast within the curettings. That brings up the possibility of an ectopic pregnancy in which the trophoblast was not accessible to the curette. The type of ectopic pregnancy in this particular patient, since the right ovary and right tube were removed eight years before admission, has to have been either left-sided ovarian, left-sided tubal or left-sided or right-sided interstitial or cornual. Those possibilities cannot be ruled out on a morphologic basis in the absence of trophoblast.

In any event, two weeks later she thought that she had a normal period because she had dysmenorrhea. On the basis of any physiologic evidence that we have, I doubt if she had a true menstrual period two weeks after the abortion. The soonest that a patient menstruates after an abortion is one month although most of them do not bleed menstrually that soon. The earliest post-partum menstrual bleeding that I know of is six weeks — that is, the patient ovulated a month after delivery and menstruated two weeks later.

Subsequently, the patient under discussion had two menstrual periods, apparently accompanied by massive hemorrhage. You all know from your history taking, however, that all patients bleed at least a cupful. Nor does it take much blood to make a great show on a towel or sheet. The level of hemoglobin later on indicated that she had not lost an excessive amount of blood during these periods of bleeding. Hormones were given. I should like to point out that it is not very good medicine, in the absence of a justifiable reason and without having investigated the inside of the uterus by surgical means, to prescribe hormones. I am sure that the patient and the physician gave the credit to the hormones for the cessation of the bleeding, but I think the cessation of the bleeding was purely coincidental.

Simple ovarian cyst is a catchall that includes several pathologic entities, one of which is the follicular cyst with atrophic epithelium. Another is a simple cystoma lined with cuboidal or columnar epithelium. This diagnosis gives no real information about the lesion removed except that it was probably benign. The removal of the tube and ovary on the right eight years before admission rules out adnexal disease to account for the right-sided bulge on the uterus.

The cytologic examination of the vaginal smear definitely rules out carcinoma of the cervix, which is not a possibility anyway, but probably does not rule out a choriocarcinoma. I have no data about what the vaginal smear in the presence of a true choriocarcinoma shows. I doubt whether that tumor would be recognized by even a competent cytologist, such as you have here. The smear does not rule out an endometrial carcinoma. Vaginal smears are positive for malignant cells in only about 75 per cent of the cases of true invasive endometrial carcinoma. The fact that the patient was thirty-seven and had had a number of pregnancies also does not rule out endometrial carcinoma. I remember a patient of twenty-three years who had a carcinoma within months after the delivery of a normal baby.

The operation, I assume, was a dilatation and curettage, alone, or followed by a hysterectomy and a salpingo-oöphorectomy on the left.

I should like to comment on the fact that packing is a little unusual after curetting for an abortion, which suggests that there was some process within either the endometrial cavity or the myometrium that was not, or could not be, reached by the curette. The packing after an abortion in the second month of pregnancy suggests a variant of the placenta accreta, either focal or partial, with retained placental tissue. It also suggests a choriocarcinoma coincidental with the pregnancy — namely, the abortion — from which it arose. I have seen examples of coincidental choriocarcinomas derived or associated with all types of pregnancy — normal, abortive, extrauterine and molar (that is, hydatiform-mole).

I doubt if it was connected with the pregnancy of three years before admission, although a latent period of three years between the pregnancy and the choriocarcinoma is possible. Usually, the interval between the pregnancy and clinical signs and symptoms of choriocarcinoma is much less than that. The evidence is accumulating that choriocarcinoma tends to be coincidental with the pregnancy that gives rise to it.

In the absence of any morphologic evidence all one can do is talk about possibilities. I shall reiterate that the patient may well have had an ectopic gestation (not all of them rupture, and not all bleed intraperitoneally). The possibilities are left-sided ovarian, left-sided tubal and either right-sided or left-sided interstitial pregnancy. If I have to make one diagnosis, however, I shall say that there was a placental polyp in the uterus. A placental polyp is not a tumor but a conglomeration of retained trophoblast, either with or without chorionic villi and with or without focal accreta, but with subinvolution of the placental site, necrosis, thrombosis and hemorrhage. Stated differently, it is the same as retained secundines without disease, other than the secondary infection, bleeding and subinvolution of the placental site. I believe that adenomyosis, which she had before she became pregnant, accounted for the menorrhagia and the dysmenorrhea. It would not surprise

me if she had a choriocarcinoma since the cases for this conference were chosen for the gynecologic postgraduate course, and Dr. Castleman knows that I have a certain interest in choriocarcinoma. I think one always has to think about "CPCmanship," if I may use a useful term.

DR. SCULLY: Dr. Curtin, will you tell us about your preoperative impression and your findings at operation?

DR. RICHARD R. CURTIN: We considered that, statistically, the most likely diagnosis was fibroid. We did not know at the time of the operation the pathological report from the dilatation and curettage done elsewhere, but I doubt if that would have changed our diagnosis. Before the operation we did a dilatation and curettage; the tissue was not peculiar, and a total hysterectomy was performed. We did not remove the left tube or ovary. At operation there was a mass in the region of the right cornu that we thought was a fibroid.

### CLINICAL DIAGNOSIS

Leiomyoma of uterus.

### DR. ARTHUR T. HERTIG'S DIAGNOSES

Placental polyp.
Adenomyosis.

### ANATOMICAL DIAGNOSIS

*Interstitial pregnancy, right.*

### PATHOLOGICAL DISCUSSION

DR. SCULLY: We received the uterus, which was opened by the surgeon in the operating room. In its wall in the region of the right cornu was a transected hemorrhagic mass that measured about 5 cm. in diameter. In the center of the mass was a cavity lined by a smooth, glistening membrane, which contained a small blood clot (Fig. 1). A short segment of right fallopian tube attached to the uterus led into the mass. Microscopically, the hemorrhagic lesion proved to be a necrotic pregnancy. The lining of the cyst was amnion. There was no evidence of an ovum. The main portion of the mass was composed of fibrin and blood clot, with scattered chorionic villi. There were a few viable syncytotrophoblast cells, but these were very rare. The thinned-out wall of the underlying uterus was chronically inflamed and extensively scarred. The endometrium away from the placenta was normally proliferative.

In the literature* it is stated that interstitial pregnancies constitute about 5 per cent of all ectopic pregnancies. They usually perforate and result in an acute surgical emergency early in their course. Occasionally, they have a clinical course of this type. There are two possible explanations for the implantation in the right tube in this case. There may have been migration of the ovum from the left ovary through the 1 cm. of right tube that the surgeon had left in eight years before, or the ovum may have entered the uterus through the left tube and been swept over into the right.

DR. HERTIG: As I mentioned in the discussion, ectopic pregnancy was a logical preoperative diagnosis because of the lack of trophoblast in the decidua. The presence of the asymmetry of the uterus is consistent with an interstitial mass rather than a fibroid.

FIGURE 1. *Transected Uterus and Conceptus. The exposed surfaces of the conceptus show the glistening amnion, beneath which is clotted blood.*

It is also consistent with a localized area of adenomyosis or "adenomyoma." I considered fibroid but did not think it explained all the symptoms that this patient had. The explanation for the fact that the pregnancy was in the remains of the right tube could be either one of the possibilities mentioned by Dr. Scully. We know that the side from which the ovum arises does not determine the side to which it will migrate; it may go over to the opposite cornu. Also, external migration is possible because we know that in so-called tubal ligation for sterilization an ostium is occasionally re-established, and the egg enters it, presumably by the motion of the current of fluid set up by the action of the cilia of the tube. All eggs are ovulated into the peritoneal cavity, not directly into the oviduct.

*Felmus, L. B., and Pedowitz, P. Interstitial pregnancy: a survey of forty-five cases. *Am. J. Obst. & Gynec.* 66:1271-1279, 1953.

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## CASE 42452

### PRESENTATION OF CASE

A twenty-eight-year-old housewife entered the hospital because of recurrent respiratory infections.

Two years previously she had a severe cough that persisted for about a year. Nine months before admission she had a severe cough with malaise for a month. An x-ray film of the chest was normal. Three months later she had a severe respiratory infection, with a cough productive of blood-tinged sputum,

that lasted for several days. X-ray films of the chest demonstrated a density overlying the right-lower-lung field, with a shift of the mediastinum to the right and obliteration of the right leaf of the diaphragm. Films taken during the next three weeks showed persistence of an area of collapse, with dilated bronchi in the region of the right lower lobe and mediastinal shift to the right; there was clearing of the generalized density that overlay the right-lung field; the posterior half of the right leaf of the diaphragm remained obliterated by the consolidation. With penicillin therapy there was an improvement in symptoms. During the two months before admission films of the chest demonstrated a return of the mediastinum to the mid-line, residual coarsened bronchovascular markings in the right lower lobe and elevation of the right leaf of the diaphragm (Fig. 1 and 2). Three weeks before entry she was admitted to another hospital because of another respiratory infection. A culture of the sputum grew out *Staphylococcus aureus*. She improved with chloramphenicol therapy.

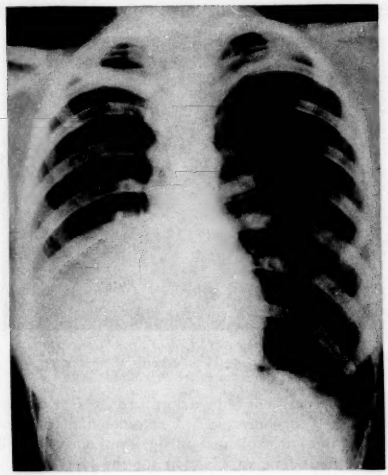

FIGURE 1. *Posteroanterior View of the Chest, Showing the Density Obscuring the Right Leaf of the Diaphragm and Right Border of the Heart, with a Minimal Shift of the Mediastinum to the Right. The right hilus is displaced inferiorly.*

Physical examination revealed a thin woman in no distress. Examination of the chest showed elevation of the right leaf of the diaphragm, with limited motion of the diaphragm on this side.

The temperature was 98.4°F., the pulse 84, and the respirations 18. The blood pressure was 124 systolic, 76 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 ml. and a white-cell count of 13,900, with 73 per cent neutrophils. The total protein was 7.5 gm., the albumin 4 gm., and the globulin 3.5 gm. per 100 ml. A culture of the sputum gave a moderate growth of alpha-hemolytic and nonhemolytic streptococci.

An operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTMAN*: I hope that the medical students to whom we lecture on diseases of the lung do not "get the idea" that the taking of histories and the performing of physical examinations are merely arts learned to pass the course in the second year. I should be in a much more secure position to arrive at a diagnosis in this case if I had more information about the physical examination. There was no mention of several things that I think are important: the expansion of the chest, which, because of the x-ray finding, I assume was diminished on the right side; resonance of the chest; the quality of breath sounds; whether breath sounds were present or absent on the right side; whether or not there were rales; and whether there was any wheeze at any time. There is no clue to whether the bronchus to the right lower lobe was open or closed, and I

FIGURE 2. *Lateral View of the Chest.*

*Associate physician, Massachusetts General Hospital.

believe that is a very important aid in arriving at a reasonable diagnosis in this case.

Now, Dr. St. Aubin, would you show us the films?

DR. PAUL M. G. ST. AUBIN: Films of the chest taken nine months before admission are within normal limits. Six months later there is a density obliterating the right leaf of the diaphragm, limited to the lower portion of the right-lung field. There is displacement of the heart to the right, some elevation of the right leaf of the diaphragm and possibly some fluid in the right pleural space. On the film taken ten days later there is an increase in the extent of the density, and the heart is still shifted to the right. Four or five days later there is some reduction in the size of the density. What is presumably the right leaf of the diaphragm is now seen. However, this shadow could represent subpulmonary fluid closely held to the right leaf of the diaphragm; the heart is again seen displaced to the right. In the lateral film it is possible to localize the process; the left leaf of the diaphragm is sharply outlined; the right leaf of the diaphragm is well seen in its anterior portion, and posteriorly there is a triangular area of density in which there are aerated bronchi, indicating that this is an area of consolidation as well as collapse. The inferior portion of the major fissure is obviously retracted back on the right. Ten days later there is definite clearing in this area. The diaphragm is more sharply outlined, as are the minimally dilated air-containing bronchi, which are surrounded by residual density. The heart is nearer the mid-line. This process gradually clears, the entire extent of the diaphragm now becoming visible. A month later there is an obvious accumulation of fluid over the diaphragm and, again, an area of collapse in the lower lobe (Fig. 1 and 2).

DR. PITTMAN: In the grid films can you follow the right main bronchus down from the carina?

DR. ST. AUBIN: The right main bronchus can be relatively well seen, and there is a suggestion of narrowing in the intermediate bronchus.

DR. BENJAMIN CASTLEMAN: Dr. St. Aubin, what lobe of the right lung would you say seems to be involved?

DR. ST. AUBIN: This must be a trap you are leading me into. The fact that in this projection the medial border of the heart is lost suggests that the middle lobe is the one involved; however, in the lateral projection the disease appears to be in the superior and probably medial segments of the right lower lobe.

DR. PITTMAN: How about the position of the right hilus in relation to the left?

DR. ST. AUBIN: The left is normal in position; the right is drawn down.

DR. PITTMAN: Is that as likely to go down with disease of the middle lobe as it is with disease of the lower lobe, the middle lobe being smaller?

DR. ST. AUBIN: No.

DR. PITTMAN: In summary, this young woman had, between the age of twenty-six and twenty-eight years, some process that either caused or laid the groundwork for repeated cough and repeated respiratory infection. The absence of any earlier history suggests to me that before the age of twenty-six she had nothing of this sort. At first, there was no change in the x-ray films and then signs of collapse, which I had thought were of the lower lobe but which perhaps were of the middle lobe, appeared — these signs being a mediastinal shift and a high diaphragm on the affected side and probably, early and again later, some fluid. I imagine that there was not a great deal of fluid, in view of the fact that the mediastinum was displaced toward that side. Subsequently, there was some return of the mediastinum toward the mid-line, which, I assume, means some re-expansion of the involved lobe.

I think that whether or not the main bronchus to the lower lobe was open is important. If that bronchus was open, the episodes probably represented pneumonitis around bronchiectasis, with the development of a small area of fluid, probably empyema, six months before admission. I shall not spend any time at all on tuberculosis or carcinoma, because I think those are irrelevant. If the bronchus was closed during this time, there was either a bronchial adenoma or a nonopaque foreign body that caused, at first, partial obstruction with infection distal to it and probably some localized bronchiectasis in the infected area. This lesion progressed to complete obstruction, either anatomical or produced by edema and inflammation around the wall in the region of the lesion. In either of these, I believe that there was a small effusion, probably an empyema. Because I do not know of any ill health before the patient was twenty-six years of age and because the only manifestation of the disease in its early phase was cough, I shall choose as my first diagnosis a nonopaque foreign body in the right-lower-lobe bronchus, with chronic pneumonitis beyond it that led eventually to collapse of the right lower lobe and a small area of empyema.

DR. JACOB C. LERMAN: What kind of foreign body do you think it was?

DR. PITTMAN: Nonopaque. Would a nutshell show in the x-ray films or not? I am not sure. I do not remember whether pistachio shells, which we found in a patient not too long ago, were seen in the x-ray films or not.

DR. CASTLEMAN: Can you help us on the foreign bodies or have you any other comments, Dr. Benedict?

DR. EDWARD B. BENEDICT: I should think that a foreign body would be comparatively unlikely, because there was no history of choking or gagging. Although a small foreign body may be aspirated without producing symptoms, it is rare and would not occur with a foreign body of large size. The nuts

usually do not show in the x-ray films. Certainly, a peanut would produce more symptoms than this woman had.

DR. PITTMAN: I do not want to belabor the point, but there is no history of anything.

DR. BENEDICT: But it is a classic history of adenoma of the bronchus.

DR. PITTMAN: Do not the adenomas tend to bleed more frequently than this did? There was bleeding only for a few days in the episode six months before admission.

DR. BENEDICT: Many adenomas do bleed more, but some bleed very little.

DR. PITTMAN: It would have to have been a very small adenoma nestling on the wall. That is the reason that I think that if we knew whether or not this woman had ever had a wheeze such as is heard with partial bronchial obstruction, it would have been quite helpful in arriving at a diagnosis.

### CLINICAL DIAGNOSIS

Adenoma of bronchus.

### DR. HELEN S. PITTMAN'S DIAGNOSIS

Foreign body in bronchus, with obstruction and pneumonitis.

### ANATOMICAL DIAGNOSES

*Adenoma of bronchus, cylindromatous type.*
Chronic pneumonitis, focal, middle and lower lobes.

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The operation mentioned in the history was a bronchoscopy done at another hospital. Dr. Wilkins, would you tell us about the operation done in this hospital?

DR. EARLE W. WILKINS, JR.: Apparently a complete work-up was done in the other hospital. The patient was bronchoscoped, and the lesion was demonstrated in the posterior basal segment of the right lower lobe. It was difficult for us to explain how the bronchoscopist could get that far down and not see anything before that level. The point that disturbed us was a report of a carcinoma on the biopsy. Our Pathology Department, however, called it an adenoma.

Operation showed collapse of both the middle and lower lobes, with a minimal amount of fluid in the pleural space. The right middle and lower lobes were resected.

DR. CASTLEMAN: In resecting the specimen Dr. Richard H. Sweet cut close to the upper-lobe bronchus; as he cut across it he felt that he was cutting through tumor, so he resected the bronchus as close to the upper-lobe orifice as he could. At the time we found that there was a permanent obstruction to the middle lobe only. The lower-lobe orifice, when we received the specimen, seemed open; we could push the adenoma up and see normal lumen of the bronchus to the lower lobe. I imagine that the tumor acted as a ball valve, at times producing collapse of the lower lobe. We were able to aerate that lobe, but the middle lobe was irreparably diseased by the obstruction. The tumor extended along the cartilaginous wall of the bronchus after the fashion of the noncarcinoid or cylindromatous type of adenoma. In other words the cylindromatous adenoma penetrates and extends, rather than remaining localized as the carcinoid type does.

DR. PITTMAN: Like the one that Dr. Soutter* described so beautifully here once?

DR. CASTLEMAN: Yes. Microscopically, the tumor contained small cells — some in acini — some of which contained secretion. We were unable to find mitoses. Some pathologists prefer to call this tumor a low-grade adenocarcinoma. These adenomas rarely metastasize, but they extend and penetrate. In this case it extended up around the bronchus farther than could be seen with the naked eye.

Dr. Wilkins, I understand that you have seen this patient recently.

DR. WILKINS: I saw her about two months after the operation. She was well. I think we have to watch carefully the remaining right main bronchus for the reappearance of disease. She should be bronchoscoped periodically.

DR. BENEDICT: I am surprised that a collapse of the right middle lobe was not demonstrated in the lateral x-ray film. Do you agree, Dr. St. Aubin?

DR. ST. AUBIN: Yes; I do.

DR. CASTLEMAN: Do you not think that it must have been present?

DR. ST. AUBIN: It could have been. With a collapsed right lower lobe the right margin of the heart is usually fairly well defined because it has the aerated middle lobe against it. The only evidence of collapse of the right middle lobe is the loss of the right margin of the heart in some of the posteroanterior films.

DR. CASTLEMAN: It is possible that at times the lower lobe was collapsed, as well as the middle lobe.

DR. ST. AUBIN: In the lateral film taken three weeks before admission there are aerated bronchi in the right lower lobe, but the density anteriorly is the shadow of the heart and probably not the right middle lobe.

*Case Records of the Massachusetts General Hospital (Case 39111). *New Eng. J. Med.* **248**:466-470, 1953.

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## A DECADE OF INTERNATIONALISM

THE agenda of the tenth general assembly of the World Medical Association, held in Havana from October 9 to October 15, included, among other major items, a discussion of the second world conference on medical education, to take place in Chicago late in the summer of 1959. It will be recalled that the first conference was held in London in August, 1953, under the sponsorship of the Association, immediately prior to the Association's general assembly at The Hague. Other items debated were hospital administration and medical care in Latin America, and an international code of medical law.

Two scientific symposiums were held, on pathology in prematurity and on cardiovascular surgery. Three subjects occupied the attention of the medical editors, who, as has been the custom since 1951, conferred together the day after the close of the assembly. These were "The Pan American Medical Publication Problem," "The Scientific Medical Article and Medical Ethics" and "The Pan American Confederation Journal As a Means of Medico-Social Advancement in Latin America."

The Assembly, regularly and faithfully convoked each year since its inception soon after the war, brings the World Medical Association itself, its composition and its functions into perennially recurring prominence. A federation of the national medical associations of 52 nations, it represents through these organizations the aspirations of more than 700,000 physicians. Its functions and accomplishments have included a strengthening and unification of the moral and ethical bonds that exist among these physicians; the championing of physicians' rights in the broad field of social security, including defensive measures against the International Labor Organization in its attempts at medical socialization; the protection of medical research and the national pharmacopoeias, and the publication of the bimonthly, trilingual *World Medical Journal*.

The permanent office of the secretariat of the Association is in New York; this office and the Association's Council are supported in large part by the United States Committee, consisting now of over 5000 American physicians who have availed themselves of this opportunity for affiliation with the Association as individuals.

The United States Committee, although it has been in existence for several years as a supporting group, met for the first time as a corporate body in June of this year. Dr. Austin Smith, chairman of the Committee and editor of the *World Medical Journal*, best known for his capable editorship of the *Journal of the American Medical Association*, presided. As a result of this meeting, at which the need for an increased membership was stressed, a bimonthly newsletter was put afoot, the first issue of which appeared in August. The meeting adjourned to a magnificent

reception and cocktail party, tendered, with benign inconsistency, by the Pepsi-Cola Company, which also presented the Committee with a silver gavel, a tangible guarantee of future meetings to come.

## ACUTE ASEPTIC MYOCARDITIS

RECENT advances in the technics of isolation and propagation of viruses have resulted in the recognition of many new groups and types of viruses from human materials and the identification of increasing numbers of them with various pathologic entities in human beings. The relation of certain of these viruses to some of the simple infections of the respiratory and alimentary tracts, to certain epidemic types of conjunctivitis and particularly to many cases of aseptic meningitis, some of which resemble nonparalytic poliomyelitis, was recently discussed in these columns.*

In this issue of the *Journal* Kibrick and Benirschke report the isolation and identification of a virus from a newborn infant who died on the seventh day of life of a diffuse myocarditis and a disseminated lesion of the central nervous system. The virus, isolated from the spinal cord, was identified as belonging to Type 3 of Coxsackie Group B. There was also serologic evidence consistent with recent infection of the mother with this virus. Viruses of Coxsackie Group B have already been established as a cause of epidemic pleurodynia and of some cases of aseptic meningitis occurring during epidemics of that disease; they have also been isolated from cases of other types of infections, as pointed out by the authors.

Kibrick and Benirschke also review some of the reports on the occurrence of pathological and clinical evidence of involvement of the myocardium in many different diseases of known viral etiology and they refer to the more recent evidence implicating some members of the Group B Coxsackie viruses in reported cases of myocarditis, including some that occurred in epidemic form. It seems highly probable that others among the new groups of viruses will prove to be causative factors in similar cases.

In the present report the possibility of an etiologic relation between the virus that was isolated and the case from which it was obtained is strengthened by the fact that this virus produced similar lesions in the myocardium and the central nervous systems of mice. Such lesions had previously been described in experimental infections of suckling mice, but their direct association with myocarditis in a human case yielding one of the viruses from diseased tissue is here described for the first time.

The authors, taking a cue from the varieties of cases of viral infections producing meningeal irritation that are described under the term "acute aseptic meningitis," suggest the use of the term "acute aseptic myocarditis" for the various nonbacterial entities that are accompanied by myocardial involvement as the major clinical or anatomic expression of the infection. In each infection a variety of etiologic agents may give rise to the same lesion, and other organs than the one indicated in the designation may be involved, but the major pathology is best described under that special designation.

*Editorial. Viruses in search of disease. *New Eng. J. Med.* **255**:100, 1956.

## FLORIDA'S HEALTH CENTER

THE Gainesville, Florida, *Daily Sun* announced on October 11 the impending dedication of the first unit — the Medical Sciences Building — of the J. Hillis Miller Health Center at Gainesville. A monument to the inspiring leadership of Dr. Miller, president of the University of Florida from 1947 to 1953, the building and the plan behind it present tangible evidence, of interest to physicians the country over, of Florida's progress in educational facilities, especially at higher levels.

The form that the Health Center has taken and its location at Gainesville are the result of a study made by the Commonwealth Fund in 1952 at President Miller's request. Both the plan and the geographic site in relation to the State as a whole represent his insistence that "the Health Center must be a part of the State and must concern itself with the training of a variety of personnel who are required to meet all the health needs of the people. In brief, the Health Center is not only a part of the University but it is a part of the local and State community."

The College of Medicine, with an initial enrollment of 47 students in the class of 1960, is designed especially for the training of family physicians to serve Florida's population; it will, however, also confer graduate degrees in the various medical sciences. The entering class of 44 young women in the School of Nursing will move into the second unit of the Center, the Teaching Hospital, when that building is completed in 1958. The third unit, now awaiting legislative approval, will be the College of Pharmacy.

In sharp contrast to the unfolding of Florida's plans for the medical education of her youth at these high levels is the story, published on the front page of the same issue of the *Sun*, of the experience of a school teacher in Jefferson County. This young woman spoke in defense of Dr. Deborah Coggins, the county health commissioner who was discharged for having broken bread with a Negro nurse† and has herself been asked to resign by the Jefferson County School Board.

†Editorial. Bread unleavened. *New Eng. J. Med.* **255**:828, 1956.

## BIOLOGIC INTERLUDE

It is common knowledge that the common cobra, *cobra de capello (Naja tripudians)*, flourishes in southern Asia and in Africa, not only in large numbers but in a number of varieties. It particularly excites the imagination because of its habit, when aroused, of elevating its cervical ribs and stretching the skin of its neck transversely into the accustomed hood. Peaceably disposed and inclined to make a household pet of itself, like the donkey in Aesop's fable, the cobra nevertheless causes over 5000 deaths annually in India and is ordinarily considered as an unwelcome tenant. In its encounters with the mongoose *(pl.* mongooses), a viverrine mammal of India, it generally comes off second best.

It is interesting to learn that the cobra, feared yet fascinating, has at last yielded the secrets of its sex life to the somewhat merciless scrutiny of modern science and the graphic arts. This invasion of its ophidian privacy is a result of the personal strategy of Sam Dunton, staff photographer of the New York Zoological Society, who not only made a color motion picture of the complete reproductive cycle of the king cobra *(N. hannah)* but projected it at a session of the twenty-sixth annual meeting of the Biological Photographic Association in Rochester, New York, last August.

The king cobra, found in its natural state from India to southern China, where it attains a 12-foot length, appears to be the original snake charmer, at least so far as its queen is concerned; in this instance the silver screen failed to respect the most intimate of relations or to spare those feelings that are instinctive with the female of any species. The first time, it is believed, that this activity of the cobra has ever been fully observed, the serpiginous symphony reveals the preliminary courtship, the mating, the nest building and the emergence of the offspring from the egg, thus elevating the cobra to that well known biologic level with which the bees, the flowers, and possibly man are ordinarily identified.

Like Minerva who sprang fully armed from the forehead of her illustrious parent, the infant serpent, ready with its fangs and venom glands, belies the peaceful nature attributed to its species by attempting to strike even before it is fully hatched into a world that on the whole dislikes cobras.

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*Dr. M. E. Winchell has resigned his position of Assistant Physician in connection with the New Jersey State Lunatic Asylum. Dr. Montgomery has resigned the Professorship of Midwifery in the School of Physic in Ireland, which he has for the long space of twenty-nine years so ably filled.*

Boston M. & S. J. *November 13, 1856*

## MASSACHUSETTS MEDICAL SOCIETY

### TOXIC HAZARDS*

#### Naphthalene Poisoning†

Naphthalene, a derivative of coal tar, is widely used in industry, with little toxic effects. Its ingestion by children, however, may result in a dramatic and occasionally fatal poisoning. The following case report from the Children's Medical Center, Boston, demonstrates the acute hemolytic anemia that this agent may produce:

L.G., a 14-month-old boy, was admitted to the hospital desperately ill after a 3-day history of mild diarrhea, temperature of 102°F., vomiting and pallor. Pink urine had been passed on the day of admission. Physical examination revealed gasping respirations, extreme pallor with slight jaundice and a palpable spleen.

Examination of the blood showed a hemoglobin of 3.7 gm. per 100 ml., a hematocrit of 11 per cent, a red-cell count of 900,000, reticulocytes of 20 per cent and a white-cell count of 60,000, with 5 per cent normoblasts and a marked shift to the left. There were 10 per cent spherocytes and marked fragmentation of the erythrocytes on smear, and Heinz bodies in the red blood cells were demonstrated by supravital staining. The serum was brown, which on spectrophotometric and chemical analysis proved to be due to methemoglobin. The direct bilirubin was 2.5 mg., and the total bilirubin 9.5 mg. per 100 ml. A Coombs test was negative, and bone-marrow aspiration showed extreme erythroid hyperplasia. Initially, the urine was pink, becoming brown on standing, with methemoglobin or methemalbumin present. This color disappeared after 24 hours. The urine gave a + + + test for albumin, with numerous hyaline and granular casts in the sediment.

Prompt treatment with packed red blood cells and intravenous administration of ACTH and antibiotics was followed in 8 hours by dramatic improvement. The patient was discharged, apparently well, on the 6th hospital day, with a hemoglobin of 10.8 gm. per 100 ml.

After admission it was discovered that the child had had access to a naphthalene-containing deodorant in the diaper pail, and had probably chewed this.

Acute hemolytic anemia has been shown to follow ingestion of naphthalene moth balls in children, and the syndrome has been reproduced experimentally in dogs.[1] Recently, other household sources of naphthalene poisoning (moth flakes and toilet-bowl deodorants) have been reported.[2]

Naphthalene is insoluble in water but, because of its high vapor pressure, may be absorbed from the stomach in certain infants and children. The toxic dose is not known but as little as one moth ball (0.5 gm.) has produced toxic symptoms. Naphthalene it-

*This is one of a series of articles published co-operatively by the Committee on Industrial Health and the Panel on Child Health of the Massachusetts Medical Society. The panel provides liaison with the Massachusetts Chapter of the American Academy of Pediatrics, whose Boston and Worcester Poison Information Centers are activities of the Committee on Accident Prevention.

†From the Boston Poison Information Center.

self, on injection into the blood stream, is not hemolytic, but some of its metabolites apparently are. Many children who ingest this substance do not exhibit toxicity; this is probably related to varying degrees of absorption.

After ingestion, vomiting, diarrhea and fever appear in one or two days, followed on the third to the fifth day by the acute hemolytic crisis as evidenced by pallor, tachypnea, mild jaundice and pigmented urine. Laboratory evidence of a hemolytic anemia is present, and kidney damage may follow. Five or six days after ingestion the hemolytic process ends, and if the patient survives this stage, recovery is rapid unless acute renal failure occurs. Heinz bodies in the red blood cells are found before the hemolytic process becomes evident and are, therefore, of prognostic value in determining in which patients hemolysis may develop.

Prompt treatment with packed red blood cells and close attention to fluid balance will usually result in survival. Cortisone or ACTH has been used in only a few cases to date but appear helpful. Children who ingest naphthalene and show Heinz bodies should probably be started on one of these steroids in an effort to prevent the hemolysis.

Moth balls, despite their odor and size, are apparently attractive to the toddler, since over 20 cases have been reported to the Poison Information Center in less than two years. Vomiting is the preferred method of removal since moth balls are usually too large to pass through a lavage tube.

Inhalation of naphthalene is relatively nontoxic, producing transient headache, irritation of the eyes and mental confusion. In laboratory animals lenticular cataracts have been produced by inhalation of high concentrations, but this has not been confirmed in man.

For many years the much safer paradichlorobenzene has also been used as a moth repellent. Irritation of the eyes and nose follow inhalation of high concentrations, but no human toxicity has resulted from acute or chronic ingestion.[3] Since both compounds are sold as moth repellents, it is necessary to ask parents to save the container to determine which has been ingested.

Since the potential toxicity of naphthalene is not generally appreciated, it is wise to warn parents to keep this tempting compound out of reach of their children. Physicians should also appreciate that naphthalene may cause an acute hemolytic process. In such cases of rapidly developing anemia due to internal blood destruction, immediate transfusions are life saving.

ROBERT J. HAGGERTY, M.D.

### REFERENCES

1. Zuelzer, W. W., and Apt, L. Acute hemolytic anemia due to naphthalene poisoning: clinical and experimental study. *J.A.M.A.* **141**: 185-190, 1949.
2. Chusid, E., and Fried, C. T. Acute hemolytic anemia due to naphthalene ingestion. *Am. J. Dis. Child.* **89**:612-614, 1955.
3. Hollingsworth, R. L., Rowe, V. K., Oyen, F., Hoyle, H. R., and Spencer, H. C. Toxicity of paradichlorobenzene: determinations on experimental animals and human subjects. *Arch. Indust. Health* **14**:138-147, 1956.

## WOMAN'S AUXILIARY

The shortage of medical social workers is, at the present, acute, and there are indications that this condition will continue to exist for the next ten years — or perhaps even longer.

At a meeting of the National Conference of Presidents and Presidents-Elect, held in Chicago on October 1, the president of the Woman's Auxiliary of the Massachusetts Medical Society, Mrs. Elizabeth V. Cheney, presented a paper emphasizing the need for recruiting medical social workers. For both men and women, this field offers many opportunities. To become a qualified medical social worker, a person must hold a bachelor's degree from an accredited college. In addition the worker should have certain personal qualities — good judgment, resourcefulness, tact, ability to work with others and so forth. The worker must learn not to do things merely to and for people but, rather, to work with them. Cost of training varies from $1,000 to $2,000 a year. Two years of supervised field work in a clinic or hospital is concurrent with study. An additional two years of study in graduate-school work culminates in the degree of master of social work.

To meet this growing need, it was recommended that auxiliary members help make high-school guidance teachers aware of medical social work by providing them with releases from the American Association of Medical Social Workers, the *Health Careers Guide Book* and catalogues from schools offering training. Films, speakers and advisers on medical social work should be provided on health-career days, which should be kept separate from general-career days. College students, particularly sophomores (but also interested seniors), should be encouraged to work in this field. Finally, auxiliary members should keep themselves informed of requirements, training schools and existing scholarships and should do what they can to help provide scholarships for qualified students who need assistance.

## BOSTON MEDICAL LIBRARY

### FROM THE CURATOR'S NOTEBOOK

Among the epoch-making books in medicine few have had a more lasting influence than *An Inquiry into the Causes and Effects of the Variolae Vaccinae . . . known by the name of the Cow Pox* (London,

1798), by Edward Jenner (1749-1823). The Library has an unusual collection of various editions of this book, as well as other monographs on vaccination published soon after Jenner's work was first issued. The first edition of *An Inquiry* is of unusual interest, for it is inscribed by Jenner "For the Rev. John Clinch from his affectionate Friend the Author." According to W. R. LeFanu, the distinguished librarian of the Royal College of Surgeons of England, London, and author of *Bio-Bibliography of Edward Jenner, 1749-1823* (London, 1951), John Clinch, one of Jenner's earliest friends, who ministered in Newfoundland as doctor and clergyman, received vaccine matter from Jenner in 1798 and deserves the credit for making the earliest vaccination in the New World. This priceless copy was presented to the Library by the late Dr. Michael F. Gavin, of South Boston, who died in 1915. It will be recalled that Benjamin Waterhouse did not receive vaccine from England until 1800 and vaccinated his son on July 8 of that year, possibly as long as two years after the Reverend John Clinch had begun to vaccinate in Newfoundland. The Library has another copy of the first edition, formerly inscribed, but unfortunately two names have been cut from the title page.

The second edition of *An Inquiry* (London, 1800) was formerly owned by Dr. John Jeffries (1744-1819), the Loyalist and surgeon in British military hospitals, who crossed the English Channel in a balloon (1785) and practiced in Boston after 1790. He assembled a fine medical library. The Library also has the third edition (London, 1801), a Latin translation published in 1799, the year after the first English edition, and a Portuguese translation issued in 1803. These books were put on exhibit in the rotunda of the Library in October, 1956.

The first printing in America of *An Inquiry* was issued at Springfield, Massachusetts, in 1802 for Dr. Samuel Cooley, a Virginia surgeon. This is referred to as having been printed in Springfield, Illinois, in LeFanu's *Bio-Bibliography,* and although the title page carries only the name Springfield, the printers, Ashley and Brewer, were well known for having printed other books at the same time in Springfield, Massachusetts. The Library does not have a copy, but there is a fine imprint in the Harvard Medical School Library.

Another book of particular interest is a large paper copy of *The Anatomy of the Thymus Gland* (London, 1832), by Sir Astley Cooper, Bart., F.R.S., serjeant surgeon to the King, consulting surgeon to Guy's Hospital and so forth. The copy is inscribed: *London, March 12th. 1833. Dr. Peirson as a proof of the pleasure & information he derived from his Society by Astley Cooper* (a felicitous expression of goodwill to the Salem physician, Abel Lawrence Peirson, who was studying with him at the time). Other books owned by Peirson have recently been donated to the Library by the Peirson family, including his *Letter Book,* containing the letter that he wrote to Morton on November 22, 1846, stating that he "twice successfully applied yr. valuable discovery, to the purpose of destroying pain in surgical operations."

## CORRESPONDENCE

### IMPROVED METHOD OF STAINING

*To the Editor:* Sections from the lesions in Case 1 and Case 3 described in the article, "Laboratory-Acquired Histoplasmosis," in the February 2 issue of the *Journal* have been restudied recently at the Armed Forces Institute of Pathology by the silver nitrate methenamine stain. This stain was described by Gömöri in 1946 and was applied by Grocott to the demonstration of fungi (*Technical Bulletin* [ASCP] 25:171 [July], 1955). In both cases bodies morphologically characteristic of *Histoplasma capsulatum* were seen whereas

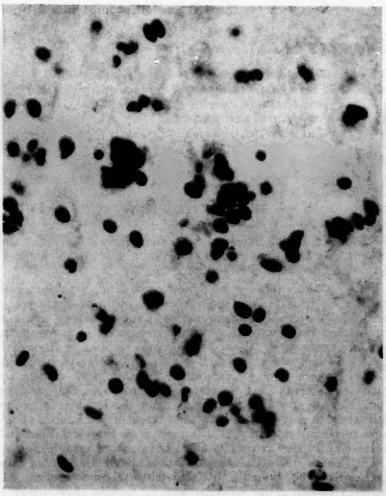

FIGURE 1.

stains used previously had not demonstrated the organisms. A high-power black-and-white print of the Gömöri stain in Case 1 (Fig. 1) is considered an excellent one by the Armed Forces Institute of Pathology. Information about the stain should be disseminated.

CHARLES G. SPICKNALL, M.D.
*Medical Director and Chief*
Medical Service
United States Public Health Service Hospital
Staten Island, New York

### INTERATRIAL DEFECTS

*To the Editor:* By this brief letter may I call attention to the fact that infants (both premature and postmature at

term) may suffer from a persistence of opening between the right atrium and the left? So many bodies examined in the dissecting room still show some aperture that it is well for clinicians (internists and also surgeons) to remember this if treatment by administration of oxygen is ordered. Certainly, oxygen cannot supply a sufficient interchange in pulmonary areas while the blood continues to pour across from the right side of the heart. Increasing the amount of oxygen may only destroy the baby's retina. Placing the baby upon its right side and elevating the shoulders, to raise the left atrium, may be the answer.

THOMAS HORACE EVANS, M.D.
Freeport, New York

### DIASTOLE OVER SYSTOLE

*To the Editor:* Re: *New Eng. J. Med.* **255**, No. 14, p. 675, lines 18-19: ". . . a blood pressure of 160 systolic, 190 diastolic."

One must hasten to mention
This state of the tension:
When higher is lower
And lower is higher,
Be quick on the trigger for prompt intervention!

WILLIAM E. NESSELL, M.D.
Springfield 2, Massachusetts

*Note:* When diastole rises above the systolic
There's something amiss more disturbing than colic
One has to be careful
And tearful and prayerful
And slow to report such a state diabolic.—ED.

## BOOK REVIEW

*Meditations on Medicine and Medical Education: Past and present.* By I. Snapper, M.D. 8°, cloth, 138 pp. New York: Grune and Stratton, 1956. $3.75.

Snapper's meditations on Dutch medicine, a subject fully familiar to him as an Amsterdamer who was professor of medicine for eight years at his alma mater before going to China and later to America, are presented with sympathy and understanding. The Boerhaavean school of the early eighteenth century at Leyden was so productive in spreading the progressive ideas of medical education that, during the thirty-seven years that Boerhaave taught, over 650 students from English-speaking countries came under his influence, ultimately to carry the clinical and scientific standards of this great physician and remarkable teacher to England, Scotland, Ireland and "the British colonies beyond the seas."

The details of Boerhaave's daily rounds in the Cecilia Hospital, where he gave his bedside lectures, encouraging students to examine the patients and to outline their ideas of treatment, following the Hippocratic tradition, are set forth in a masterly style. Due emphasis is placed on his integration into the curriculum of his "Lectures on Medical Institutes," a discussion of physics, chemistry, biology and physiology and the clinical application of the results of physiologic research.

Boerhaave thus organized a new system of teaching clinical medicine, quickly to be transferred to Germany by Albrecht von Haller, to Austria by Gerard van Swieten and Antoni de Haen and to Britain by Cullen, Pringle, Huxham and Alexander Monro, to form the great school at the University of Edinburgh, where the whole faculty was formerly trained by Boerhaave in the Leyden clinic. These Edinburgh professors in turn taught "Boerhaave's medicine" to a large group of American physicians, and the first medical school in the American colonies, opened in 1765 by John Morgan and William Shippen in Philadelphia, was modeled after the school in Edinburgh. Thus, Edinburgh, the daughter of Leyden, transmitted to Philadelphia, the daughter of Edinburgh and the granddaughter of Leyden, the spirit of new clinical medicine, and Boerhaave's influence was strongly felt in America.

Unfortunately, the sound pattern of Leyden was soon lost in the rapidly expanding United States. Ill conceived medical schools were patched together, and teaching became routine, static and frequently commercialized. It took the *Flexner Report* in 1908 to call attention to the many abuses that encompassed medical education in the early twentieth century, for only a few schools were firmly organized on ethical principles, and many were hardly more than "diploma mills." Slowly adjustments were made, poor schools disappeared, and standards were raised in the better ones, until a high degree of efficiency was obtained. But, as Snapper says, "Sound and progressive medical education is like a delicate plant which requires continuous attention." Schools and hospitals rapidly lose their reputation as a result of a malorientation of correct guiding policies. "When true clinicians who are at the same time actively interested in research will again have the opportunity to develop, the progress of medicine may well be even more propitious and medical education still better than in our times." To reach this goal, Snapper wisely points out that certain Boerhaavean principles of medical education, particularly the use of professorial demonstrations of instructive patients, will have to be revived, and medical leaders, particularly full-time teachers, should be sufficiently unburdened from their administrative duties.

HENRY R. VIETS, M.D.

## BOOKS RECEIVED

**The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.**

*Occupational Health Nursing.* By Mary Louise Brown, R.N., M.A., assistant professor of public health, Yale University School of Medicine; in association with John Wister Meigs, M.D., associate professor of public health, Yale University School of Medicine. 8°, cloth, 276 pp., with 2 tables. Springer Publishing Company, Incorporated, 1956. $4.50.

*Anxiety and Magic Thinking.* By Charles Odier, M.D. Translated by Marie-Louise Schoelly, M.D.; and Mary Jane Sherfey, M.D. 8°, cloth, 303 pp. New York: International Universities Press, Incorporated, 1956. $5.00.

*The Spine: Anatomico-radiographic studies: Development and the cervical region.* By Lee A. Hadley, M.D., senior attending roentgenologist, Syracuse Memorial Hospital, clinical associate professor of public health, New York State College of Medicine, and consultant in radiology, Syracuse State School. 8°, cloth, 156 pp., with 121 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $6.50.

*Management of Emotional Problems in Medical Practice.* Edited by Samuel Liebman, M.D., medical director, North Shore Health Resort, Winnetka, Illinois, and clinical assistant professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 152 pp., with 12 tables. Philadelphia: J. B. Lippincott Company, 1956. $5.00.

*Diagnosis and Treatment of Peripheral Vascular Disorders.* By David I. Abramson, M.D., professor of physical medicine and head, Department of Physical Medicine and Rehabilitation, and professor of medicine, University of Illinois College of Medicine, chief of physical medicine and rehabilitation, University of Illinois Research and Educational

Hospitals, attending physician, Michael Reese Hospital, Mount Sinai Hospital and Veterans Administration Hospital (Hines), and consultant in peripheral vascular disorders, Regional Office, Veterans Administration, Chicago. 4°, cloth, 537 pp., with 82 illustrations and 18 tables. New York: Paul B. Hoeber, Incorporated, 1956. $13.50.

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*Ulcers of the Legs.* By Pedro Piulachs, M.D., chief professor surgeon in the Faculty of Medicine of Barcelona. 4°, 574 pp., with 303 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $15.50.

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*Surgery of the Hand.* By Sterling Bunnell, M.D., consultant to the Surgeon General of the United States Army and United States Navy, and the Alaska Department of Health. Third edition. 4°, cloth, 1079 pp., with 1047 illustrations and 9 color plates. Philadelphia: J. B. Lippincott Company, 1956. $22.50.

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*Annual Epidemiological and Vital Statistics, 1953.* World Health Organization. 4°, paper, 572 pp., with 74 tables. Geneva: World Health Organization, 1956. £2. 10s., Sw.fr. 30.-$10.00. Bilingual edition (French and English). (Distributed in the United States by Columbia University Press, New York City.)

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*The Drug Addict as a Patient.* By Marie Nyswander, M.D., senior supervising psychiatrist, Post Graduate Center for Psychotherapy, and consultant, New York City Department of Health. 8°, cloth, 179 pp. New York: Grune and Stratton, 1956. $4.50.

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*Psychotherapy and Delinquency.* By William McCord, Ph.D., instructor in social psychology and general education, Harvard University; and Joan McCord, Ed.M., research assistant, Laboratory of Human Development, Harvard University. 8°, cloth, 230 pp. New York: Grune and Stratton, 1956. $6.50.

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# NOTICES

## ANNOUNCEMENTS

Dr. Morris Ringer announces the removal of his office to 851 Beacon Street, Newton Center 59, Massachusetts, for the practice of internal medicine.

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Dr. Richard J. La Vigue announces the addition of Dr. J. Lincoln Cain as associate, in the Medical Arts Building, 80 Grove Street, Fitchburg, Massachusetts, Burbank Hospital and Groton Community Hospital for the private and hospital practice of radiology.

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Dr. James M. McNulty announces the removal of his office to 1180 Beacon Street, Brookline, for the practice of general surgery.

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## SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 20, at 12 noon.

Dr. Nathan L. Fineberg will talk on "Management of Common Nasal Problems." All physicians are cordially invited to attend.

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## HARVARD MEDICAL SOCIETY

A symposium on aldosterone will be given by the Harvard Medical Society in the Amphitheater of Building D, Harvard Medical School, on Tuesday, November 20, at 8 p.m. Dr. George W. Thorn will preside. The program is as follows:

Introduction. George W. Thorn.

The Determination of Aldosterone and Related Compounds in Biologic Fluids. Don H. Nelson.

Factors Contributing to the Regulation of Aldosterone Secretion in Man. Eric J. Ross.

Effect of Salt and Water Excretion of Aldosterone and Diuretic Hormones Infused Directly into the Renal Artery. A. Clifford Barger and J. F. Pulenko.

Interference with Aldosterone Biosynthesis by Anphenone in Man. Jean Crabbé.

Clinical Syndromes Associated with Hypoaldosteronism. Albert E. Renold.

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## ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The annual meeting of the Association for Research in Nervous and Mental Disease will be held at the Hotel Roosevelt, New York City, on December 7 and 8.

The subject of the meeting will be "The Brain and Human Behavior."

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## AMERICAN ACADEMY OF DENTAL MEDICINE

The eleventh midyear meeting and luncheon of the American Academy of Dental Medicine will be held at the Hotel New Yorker, New York City, on Sunday, December 2.

The business meeting for members will be held at 10:30 a.m., followed by the luncheon for members and friends at 12:30 p.m. The afternoon session will feature a symposium on "Recent Concepts on the Temporomandibular Joint in Relation to Fixed and Removable Dentures and Roentgenographic Interpretation."

All members and interested dentists and physicians are invited. Further information may be obtained from Dr. A. Reiner, Chairman, 114-01-201st Street, St. Albans 12, New York, or Dr. Andrew Cannistraci, Treasurer, 2152 Muliner Avenue, Bronx, New York.

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## BAHAMAS MEDICAL CONFERENCE

The Bahamas Medical Conference will be held at the Princess Margaret Hospital, Nassau, Bahamas, December 1-15. Clinical demonstrations and lectures will be presented.

Reduced hotel rates have been arranged for participants and their families. For tax purposes, a certificate will be issued to doctors taking part in the conference. The registration fee is $75.

Further information may be obtained from Dr. B. L. Frank, Suite 1-3, 4th Floor, 550 Fifth Avenue, New York 36, New York.

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## SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 9, 1956-APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

NOVEMBER 9. American College of Obstetricians and Gynecologists. Page 731, issue of October 11.

NOVEMBER 12-16. American Public Health Association. Page 675, issue of October 4.

NOVEMBER 13, 20 and 29 and DECEMBER 4 and 18. Boston City Hospital House Officers' Association. Page 875, issue of November 1.

NOVEMBER 13-29. Consultation Clinics for Crippled Children in Massachusetts. Page 828, issue of October 25.

NOVEMBER 14 and 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.
NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 15 and JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.
NOVEMBER 20. Harvard Medical Society. Page 923.
NOVEMBER 20. South End Medical Club. Page 923.
NOVEMBER 28. Phi Delta Epsilon. Page 831, issue of October 25.
NOVEMBER 28. Middlesex County Sanatorium. Page 831, issue of October 25.
NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.
DECEMBER 2. American Academy of Dental Medicine. Page 923.
DECEMBER 7 and 8. Association for Research in Nervous and Mental Disease. Page 923.
DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

## CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 15

THURSDAY, NOVEMBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A. Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Thoracic Service Presents Cases of Medical and Surgical Interest. Dr. Wendell J. Thrower. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, NOVEMBER 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Sulfonylurea Compounds. Dr. Raffael Camerini. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, NOVEMBER 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Cerebral Blood Flow. Dr. Eugene Robin. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. (A) Fluid and Electrolyte Therapy in Pediatric Anesthesia. (B) Specialized Equipment for Pediatric Anesthesia. Dr. Smith. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, NOVEMBER 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
12:00 m.–1:00 p.m. Mortality Meeting (staff members only). Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, NOVEMBER 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess B. New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.